Differentiating and Predicting Children's Reading Skills based on Neuroimaging Data

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SILVIA BACH

of Neuenhof AG

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Prof. Dr. Lutz Jäncke

and

Prof. Dr. Daniel Brandeis

(Druckerei Irchel Zürich)

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SUMMARY

In our society, reading is a fundamental skill because the written word is a main form of communication. In the first year at school, a child learns how letters correspond with speech sounds and starts to concatenate the sounds of letters: the child learns to read. Through letter-sound decoding (grapheme-phoneme decoding) and blending, the child finally obtains a phonological representation that allows him or her to attain the meaning of a given word. During the course of reading acquisition, the reading process becomes increasingly automated, and after a while, the visual characteristics of a word alone are usually sufficient to directly and spontaneously understand the meaning of the written word.

Not all children learn to read easily, approximately 5-10% of school children struggle with learning to read and write and are diagnosed with developmental dyslexia. Research on developmental dyslexia has been done for many decades, but the etiology and the precise pathomechanism are still unclear. There are several theories about which stages are deficient in the processes of learning to read. At present, problems in phonological processing are seen as the core deficit of dyslexics as these children often struggle to recognize, differentiate, store and recall linguistic information.

In this PhD thesis behavioural and neuroimaging data were acquired and assessed in kindergarteners before and after training grapheme-phoneme-associations with a non-commercial computerized game (Graphogame) and two years later when the children were in second grade. Two main aims were pursued during this longitudinal study, which are detailed in Chapters 2 and 3 and summarized below. First, the differences in the activation of brain networks implicated in demanding phonological processing between normal and poor reading 2nd graders were characterized by using functional magnetic resonance imaging (fMRI). Then the predictive value of specific neuroimaging measurements from electroencephalography (EEG) and fMRI in non-reading kindergarteners for predicting reading outcome at school age was examined.

Chapter 2 describes the differences in the brain activation between normal and poor readers when performing a phonologically challenging letter substitution task during

fMRI recordings. The mental substitution of letters in briefly presented words and pseudowords triggered phonological processing compared to a control task. Activity referring to phonological processing was found in the left frontal cortex with maxima in the left inferior frontal gyrus (IFG) and the insula and was stronger in children exhibiting normal reading skills. Furthermore, a group difference was found pointing to more activity in the IFG in children with normal reading skills. Normal and poor reading children also differed regarding the lateralization of active regions as poor readers showed a more bilateral activation pattern as compared to the left lateralized activation pattern of normal readers. The bilateral activity has been interpreted as demonstrating the effort of poor readers to compensate the phonological and reading deficits. The difference in the functional activation of reading networks between normal and poor reading children indicates that the functional and/or neural constitution is crucial for reading success from the very beginning. Inefficient strategies thus seem to develop parallel to reading acquisition. Whether it is possible to find neural deficits earlier in development and whether such measures of brain function at preschool age are able to predict normal and poor reading outcomes in the 2nd grade was further investigated and is described in Chapter 3.

In Chapter 3, we report on the significant contribution of specific neuroimaging measurements collected in kindergarten for predicting reading outcome in the 2nd grade. During Graphogame training kindergarteners acquired initial grapheme decoding and letter knowledge that lead to plastic changes in the brain seen in the altered brain activity when processing words before and after training, although the children largely remained non-readers. The data showing the learning related emergence of print sensitivity in young children is described elsewhere (Brem et al. 2010). For prediction analyses, we used an active word processing task after training and recorded EEG and fMRI data. A differential negativity over posterior occipito-temporal electrodes in the event-related potential (ERP) to words vs. control stimuli pointed to early visual stimulus categorization and emerging print sensitivity. This N1 ERP together with the corresponding fMRI activity within the visual word form system (VWFS) of the occipito-temporal cortex were chosen as predictors as this region has been associated with print processing and has also been reported to show differences between poor and normal readers. For the first time we showed that combining predictors acquired with different methods such as behavioural,

electrophysiological as well as fMRI data significantly improved prediction of reading in the 2nd grade as compared to behavioural data alone. Furthermore, the children showing poor reading skills in the 2nd grade could already be identified in kindergarten with a high level of classification accuracy.

In summary, this thesis shows functional differences among normal and poor reading children with hypoactivation in the frontal cortex and a more distributed bilateral network in poor reading 2nd graders during phonological processing compared to a left lateralized network in normal readers. These findings indicate that compensatory strategies develop in parallel with the acquisition of reading. In kindergarteners, with behavioural data and measurements of the corresponding occipito-temporal region acquired by EEG and fMRI during reading attempts, the reading outcome in the 2nd grade was predicted and the discrimination of normal and poor reading was achieved with a high level of classification accuracy.
These results are very important as they indicate the need for early intervention, right from the start of school before compensatory strategies have emerged. It is therefore necessary to predict reading problems even before reading skills are acquired. Specific neuroimaging measurements together with behavioural data provide good markers for detecting future poor readers.

ZUSAMMENFASSUNG

In unserer Gesellschaft hat die Lesefähigkeit einen sehr hohen Stellenwert, weil häufig über schriftliche Informationen kommuniziert wird. Im ersten Schuljahr lernen die Kinder die Korrespondenz von Buchstaben und Lauten und beginnen die Buchstabenlaute zu verbinden: die Kinder lernen zu lesen. Über die sequentielle Buchstaben-Laut Dekodierung (Graphem-Phonem-Dekodierung) und Verknüpfung gelangt das Kind zu einer phonologischen Repräsentation, die dem Kind ermöglicht, die Bedeutung des Wortes zu erlangen. Im Verlauf des Leselernens wird der Leseprozess automatisiert und nach einer Weile wird aufgrund der blossen visuellen Darstellung eines Wortes meist sofort und direkt die Wortbedeutung erlangt.
Nicht allen Kindern gelingt das Lesen mühelos, ca. 5-10% der Schulkinder haben Schwierigkeiten, das Lesen und Schreiben zu lernen und werden als dyslexisch diagnostiziert. Forschung zur Entwicklungsdyslexie wird seit Jahrzehnten betrieben, jedoch sind die Ätiologie sowie der genaue Pathomechanismus noch unklar. Es gibt verschiedene Theorien darüber, welche Verarbeitungsschritte im Prozess des Lesenlernens defizitär sind. Gegenwärtig werden phonologische Verarbeitungsschwierigkeiten als das Hauptproblem bei der Lese-/Rechtschreibstörung betrachtet, d.h. die Kinder haben häufig Mühe im Erkennen, Differenzieren, Speichern und Abrufen von sprachlichen Informationen.

In dieser Doktorarbeit werden Verhaltensdaten und bildgebende Daten untersucht, die im Kindergarten vor und nach einem Training von Grapheme-Phoneme-Assoziationen durch ein nicht kommerzielles Computerspiel (Graphogame) erfasst wurden. Zwei Jahre später wurden diese Daten in der zweiten Klasse erneut erfasst. Zwei Hauptziele wurden in dieser Längsschnittstudie verfolgt, welche in den Kapiteln 2 und 3 detailliert zusammengefasst sind. Einerseits wurden Aktivierungsunterschiede in den Netzwerken des Gehirns zwischen normal und schwach lesenden Zweitklässlern bei anspruchsvoller phonologischer Verarbeitung charakterisiert, die mittels funktioneller Magnetresonanztomographie (fMRT) erhoben wurde. Andererseits wurde die Vorhersagekraft von spezifischen bildgebenden Massen nichtlesender Kindergärtner aus Elektroenzephalographie (EEG) und fMRT für spätere Lesefähigkeiten im Schulalter untersucht.

In Kapitel 2 werden die Unterschiede in der Hirnaktivierung zwischen normalen und schwachen Lesern beschrieben während sie eine herausfordernde phonologische Substitutionsaufgabe in der fMRT lösten. Die mentale Substitution von Buchstaben in kurz präsentierten Wörtern und Pseudowörtern triggerte phonologische Verarbeitungsprozesse im Vergleich zur Kontrollaufgabe. Aktivität im Bezug auf diese phonologische Verarbeitung zeigte sich in einem links frontalen Aktivierungsmuster mit einem Maximum an Aktivität im linken inferioren frontalen Gyrus (IFG) und der Insula und war stärker für Kinder mit normalen Lesefähigkeiten. Des Weiteren ergab sich ein Gruppenunterschied der signifikant mehr Aktivität im IFG bei normal lesenden Kindern zeigte. Normale und schwach lesende Kinder unterschieden sich auch im Bezug auf die Lateralisierung aktiver Regionen, da schwach lesende Kinder ein bilaterales Aktivierungsmuster im Vergleich zu einem links lateralisierten Aktivierungsmuster bei normalen Lesern aufwiesen. Die bilaterale Aktivierung wird dahingehend interpretiert, dass schwache Leser mehr Aufwand betrieben, um die defizitären phonologischen Prozesse sowie Leseprozesse zu kompensieren. Die Unterschiede in den funktionellen Aktivierungen der Lesenetzwerke zwischen normal und schwach lesenden Kindern deuten darauf hin, dass die funktionelle und/oder neurale Konstitution für den Leseerfolgt von Anfang an ausschlaggebend ist. Ineffiziente Strategien scheinen sich also parallel mit dem Leseerwerb zu entwickeln. Ob neurale Defizite bereits früher in der Entwicklung festzustellen sind und ob solche Hirnfunktionsmasse im Vorschulalter die Vorhersage von normalem und schwachem Lesen in der zweiten Klasse erlaubt wurde weiter untersucht und ist in Kapitel 3 beschrieben.

In Kapitel 3 berichten wir über den signifikanten Beitrag von spezifischen bildgebenden Massen, welche im Kindergarten erhoben wurden und eine Vorhersage von Lesefähigkeiten in der 2. Klasse ermöglichten. Während des Graphogame Trainings haben sich Kindergartenkinder erste Kenntnisse über das Graheme dekodieren und Buchstabenkenntnisse angeeignet, welche zu plastischen Veränderungen im Gehirn führten, was in der veränderten Hirnaktivität bei der Wortverarbeitung vor und nach dem Training beobachtet wurde, obwohl die Kinder immer noch nicht lesen konnten. Die Daten, welche im Bezug auf das Lernen die hervorgehende Schriftsensitivität in jungen Kindern zeigen, werden anderswo berichtet (Brem et al. 2010). Für die Vorhersage haben wir während einer aktiven Wortver-

arbeitungsaufgabe Daten der Kinder mittels EEG und fMRT aufgenommen. Ein Unterschied in der Negativität über posterioren okzipito-temporalen Elektroden im Ereigniskorrelierten Potential (EKP) bei Wörtern vs. Kontrolstimuli deutet auf eine frühe visuelle Stimuluskategorisierung und entstehende Schriftsensitivität. Dieses N1 EKP zusammen mit der korrespondierenden fMRT Aktivität innerhalb des visuellen Wortform Systems (VWFS) im okzipito-temporalen Kortex wurden als Prädiktoren ausgewählt, weil diese Region mit Schriftverarbeitung assoziiert wird und Unterschiede zwischen normalen und schwachen Lesern berichtet werden. Wir zeigen zum ersten Mal, dass die Kombination von mittels verschiedenen Methoden erfasster Prädiktoren wie Verhaltensdaten, elektrophysiologischen und fMRT Massen die Vorhersage der Lesefähigkeit in der zweiten Klasse gegenüber blossen Verhaltensmassen signifikant verbessert. Ausserdem konnten Kinder, welche in der zweiten Klasse schwach lesen, schon im Kindergarten mit einer hohen Klassifikationsgenauigkeit identifiziert werden.

Zusammenfassend werden in dieser Arbeit funktionelle Unterschiede zwischen normalen und schwach lesenden Kindern berichtet, mit Hypoaktivierung im frontalen Kortex und einem mehr bilateralen Netzwerk bei schach lesenden Zweitklässlern im Vergleich zum linkslateralisierten Netzwerk bei normalen Lesern während phonologischer Verarbeitung. Diese Befunde weisen auf Kompensationsstrategien hin, welche sich parallel zum Leseerwerb entwickeln. Im Kindergarten konnte die Vorhersage von Lesefähigkeiten sowie die Diskriminierung von normalem und schwachem Lesen in der zweiten Klasse mit hoher Klassifikationsgenauigkeit mittels Verhaltensdaten und Massen der korrespondierenden okzipito-temporalen Region im EEG und fMRT während Leseversuchen erbracht werden.

Diese Resultate sind sehr wichtig, weil sie auf die Notwendigkeit von frühen Interventionen hinweisen, die mit dem Schulbeginn am meisten Nutzen bringen, da sich Kompensationsstrategien noch nicht entwickelt haben. Darum ist eine frühe Vorhersage von Leseproblemen noch vor dem Leseerwerb nötig. Spezifische bildgebende Masse zusammen mit Verhaltensdaten können gute Marker liefern, um zukünfig schwache Leser ausfindig zu machen.

LIST OF ABBREVIATIONS

EEG	electroencephalogram
ERP	event-related potential
fMRI	functional magnetic resonance imaging
GFP	global field power
MANOVA	multivariate analysis of variance
MMN	mismatch negativity
VWFA	visual word form area
VWFS	visual word form system
ROI	region of interest
LOT	left occipito-temporal
IFG	inferior frontal gyrus
MFG	middle frontal gyrus
MTG	middle temporal gyrus

1 INTRODUCTION

Reading is one of the most important cultural communication and knowledge acquisition techniques in our society. Our school system is very much based on written information and reading ability is essential for educational success. Even though some children develop an early interest in learning letters, in Switzerland reading is not taught in kindergarten. The children start formal reading instruction when they enter school at age 7. They first learn grapheme-phoneme associations followed by blending letters and their corresponding phonemes until a phonological representation of a given word allows lexical access. Some children, however, struggle significantly with learning to read despite normal intelligence and are diagnosed with dyslexia (for more information about the definition of dyslexia see chapter 1.3.2). There is broad consensus that difficulties in reading, writing and spelling skills are mainly caused by a reduced phonological awareness. Even though problems in reading can be vaguely predicted by a child's precursor skills such as phonological awareness or letter naming at preschool age, this prediction is often insufficient or imprecise. Logopedic interventions at this age are usually only administered when the child exhibits clear expressive language problems that may also impede learning to read. Dyslexia is only diagnosed after the start of school, at the end of the 2nd grade or at the beginning of the third grade. However, interventions are most successful when applied as early as possible, when formal reading instruction starts or even earlier, before less efficient strategies develop. Unfortunately, by the time a child is first diagnosed as dyslexic, he or she has already established and developed some deficient representations/skills. Therefore, it is a general aim to detect emerging reading problems as early as possible to initiate individual support in order to prevent severe reading deficits as well as social, emotional and behavioural problems.

Within this thesis, we used multimodal, non-invasive methods (EEG and fMRI) to investigate language processing and the (dys)function in underlying brain networks of children exhibiting normal and abnormal reading development. The EEG measures are derived from the scalp and represent the electric activity of large neuronal populations. The advantage of this method is an excellent time resolution (milli-seconds), however the spatial resolution is poor. The fMRI, in contrast, provides a high spatial resolution (in mm^3) but a low time resolution. This method relies on blood

perfusion changes induced by neuronal activity and thereby enables the identification of brain regions involved in cognitive processing. One of our aims was to determine differences in the neural networks of normal and poor readers during phonological decoding processes in the 2nd grade. Further, the data from kindergarten was analysed to define specific markers predicting poor reading outcome in the 2nd grade. The following sections first give an overview over the used imaging methods to offer context information about data acquisition and analyses in our studies. Thereafter, a short summary of the most important findings of EEG and fMRI studies on word processing, phonological processing and prediction of dyslexia is given.

1.1 Electroencephalography (EEG)

1.1.1 Basics of EEG

In 1929, Hans Berger was the first to report on measurements of the human EEG. Today, the electroencephalography (EEG) is important for many clinical applications such as in diagnosing epilepsy (Zschocke 2002). It also provides important information about cognitive processing when recording the event-related electro-physiological responses time locked to a particular stimulus or response (Luck 2005). During the non-invasive EEG recordings, the signals of one or more electrodes placed on the scalp are usually recorded to a common reference electrode (but also a combination of sensors, such as linked mastoids, often serve as a common reference). Since no location on the scalp has a zero-potential and thus can act as a true reference point, an average reference over all scalp electrodes is often computed (Lehmann 1980) off-line. The position of the electrode arrangement is generally based on the international 10-20 System (Jasper 1958), a standardized configuration, which refers to four reference points: the inion, nasion and the pre-auricular points. After the recordings the acquired raw data is processed to eliminate artefacts. Standard post-processing includes filtering as well as rejection of large artefacts and exclusion or correction of eye movements (e.g. blinks). The EEG is an instrument with a high temporal resolution while its spatial resolution is rather low, even though it slightly increases with additional electrodes and better coverage of the scalp potential field.

The EEG is not sensitive enough to measure activation occurring in one neuronal cell, but measures summed electrical activity of populations of neurons. Neurons have intrinsic electrical properties and are excitable. When they are activated they produce electrical fields, which can be recorded by the electrodes on the scalp. The recording is based on changes in the postsynaptic potentials of neurons either caused by synaptic excitation (excitatory postsynaptic potential: EPSP) or inhibition (inhibitatory postsynaptic potential: IPSP). An action potential is evoked and transferred along the axon if an excitation occurs. Neurotransmitters are released into the synaptic cleft and change the membrane potential of the postsynaptic cell, which initiates the postsynaptic potential. Such postsynaptic potentials can summate across parallel (typically pyramidal cortical) neurons to polarize extended brain regions. This neural mass activity can be detected at the scalp as an EEG, because the corresponding currents are volume-conducted through the different layers of tissue in the brain, such as the meninges, skull and scalp (Michel et al. 2009; Zschocke 2002).

1.1.2 Event-related-potentials (ERP)

To measure cognitive processes the responses to repeated trials to e.g. an external stimulus are recorded. The time-locked responses to sensory, motor or psychological events are called event-related potentials (ERPs). Spontaneous EEG oscillations have amplitudes of around 10-100μV but the ERPs have much smaller amplitudes of around 0.1-20μV (Dawson 1951). Only by repeating events can the signal-to-noise ratio be increased through averaging, and the characteristic neural response to the stimulus can be extracted. The ERP components represent a waveform with peaks and troughs that are usually labelled according to their polarity (N=negative; P=positive) and time of occurrence. The time is either indicating the time in ms after stimulus presentation or the sequence of positivity/negativity (e.g. N1=first negativity after stimulus presentation). Components that are often examined in cognitive neuroscience are the P100, N100, P300 and N400. In visual studies, the P100 activation shows characteristic positive deflections over the occipital cortex pointing to early visual processing arising from the extrastriate occipital cortex (Di Russo et al. 2003; Martinez et al. 1999). The visual N100 within 150ms – 200ms has been characterized as a prominent left hemispheric negativity at occipito-temporal

electrode sites and is enhanced for specific categories of images such as numbers, letters and faces (Tarkiainen et al. 2002). It has consistently been reported, that N100 responses contribute to facial feature detection (Latinus and Taylor 2006; Tarkiainen et al. 2003). But the perception of pictures (Doniger et al. 2001), shapes (Curran et al. 2002) or objects (Wang and Suemitsu 2007) have also been reported to influence the visual expertise and enhance the N100. The P300 has been reported to be involved in the evaluation and comparison of the stimuli in respect to one's expectations (Hajcak et al. 2005; Sato et al. 2005). Therefore the duration of the P300 has been used as a measure of evaluation processes, measured at fronto-central electrodes (Hajcak et al. 2005). Others also ascribe attentional processes or estimations of the meaning of a stimulus to the P300, as the amplitude varies depending on the subject's categorization of the stimuli. The N400 component is characterized by a negativity at centroparietal electrode sites and has typically been found in association with semantic tasks. Sentence endings with a contextual incongruent word, for example, induce larger N400 negativities (Kutas and Hillyard 1980).

1.1.3 ERP topography

When ERPs are recorded from multiple sites and referred to a common reference the topographic distribution of the potential fields over the scalp can also be analysed at a given time in respect to an event. According to Lehman et al. (Lehmann 1987) these distributions can be viewed as landscape-like maps in which values between the actually measured sites are interpolated. Multiple ERP maps with continuous points in time may be displayed as a series of maps to elucidate changes in topography and strength in time. The location of maxima and minima in these maps as well as the latencies are independent of the reference, however the amplitude and topography are not, as these are shifted by a constant magnitude regarding the reference. After an average reference has been calculated, the strength of a potential field can be indexed by the global field power (GFP) which is defined as the root mean square (RMS) of the voltages from all electrodes at a specific time point (Lehmann and Skrandies 1980).

1.1.4 ERP source localization

ERP maps contain spatial information about the electric field on the scalp, but no information about the location of the electrophysiological sources in the brain. By a known source configuration the scalp electromagnetic fields can non-ambiguously be produced by complex geometry and the knowledge of different conduction properties of the tissue in the brain: this is called the forward problem. In contrast, the inverse problem consists of finding the sources in the brain that explain the activity recorded at the scalp. As an unlimited number of source configurations can induce equal electromagnetic activity on the scalp, the inverse problem is difficult to solve and requires additional assumptions. There are two main approaches to the inverse problem: dipole modelling and distributed source modelling. For dipole modelling a predefined number of point sources estimates their location (Scherg and von Cramon 1985). Source modelling such as low-resolution electromagnetic tomography (LORETA) computes the smoothest of all possible 3-dimensional current source distributions that produce precisely the measured potential field. This smoothness implies that neighbouring neurons must be simultaneously and synchronously active and produce blurred images. Therefore, the resulting tomography delivers a relatively low spatial resolution (usually <1cm) (Pascual-Marqui et al. 1999; Pascual-Marqui et al. 1994). Both approaches, dipole source modelling and LORETA, use spherical head models for their calculation.

1.2 Functional Magnetic Resonance Imaging (fMRI)

1.2.1 Basics of fMRI

The functional magnetic resonance imaging (fMRI) is a non-invasive imaging technique sensitive to the magnetic properties of the blood (haemoglobin). The magnetic properties of haemoglobin depend on whether it is bound to oxygen. De-oxygenated blood has paramagnetic properties, which means that it is more sensitive to a magnetic environment in the scanner as compared to diamagnetic oxygenated blood. Therefore, the deoxygenated blood decreases the MR signal. The signal measured by the MR scanner is dependent on the ratio between oxygenated and deoxygenated blood, which is called the blood oxygenation level dependent contrast

(BOLD). During neuronal activity the MR signal increases as the ratio between oxygenated and deoxygenated blood changes by the disproportionately high delivery of oxygen compared to the consumed oxygen. About 2 seconds after the stimulus presentation the deoxygenated haemoglobin shows a peak in the rise and then rapidly declines until after 6 seconds when it falls below the pre-stimulus level. On the other hand, oxygenated haemoglobin rises slower but peaks higher at about 5 to 6 seconds after stimulus presentation (Huettel et al. 2003) and returns to baseline after 10 to 16 seconds. The fMRI method provides brain activation images, showing which brain areas are active during a specific task in relation to a control condition or baseline activation by the indirect mapping of cortical activity through the BOLD signal change (hemodynamic response).

1.2.2 FMRI activation

Stimuli from different conditions can be randomly presented and analysed separately. As with the ERPs, stimuli are presented repeatedly. Generally, after the recording, the time course of the MRI signal change is modelled. For fMRI data analysis the most common strategy relies on fitting a general linear model (GLM) to the data (Friston et al. 1994). A GLM is a set of equations expressing the predicted time course of the fMRI signal as a weighted sum of linear terms displaying the effects of interest and confounds (Mulert and Lemieux 2010). The linear model is correlated with the actual signal sequence of each voxel in the brain, thereby relating fMRI changes to the experimental effects. In some voxels the correlations are significant, which means they show an increased signal during the task (Jäncke 2005). Linear combinations of coefficients are called contrasts. Usually an experimental condition measuring responses to a specific stimulus is compared to a control or baseline condition by testing the statistical significance of the contrasts with a t-statistic (Mulert and Lemieux 2010).
Furthermore, hemodynamic responses of specific functional or spherical regions of interest (ROI) can be defined and their signal change can be extracted and analysed, for example, by testing for group differences or correlations with behavioural data.

1.3 Reading and Dyslexia

1.3.1 Learning to read

In our society, reading is an essential form of communication and thus we are confronted with letters from early childhood on. Even before we can read we encounter print from e.g. poster sites or advertisements. Many children learn to read and spell easily. Others however struggle from the very start when learning the alphabetic principle that involves knowledge of grapheme-phoneme correspondences which in turn affect reading accuracy (Katzir et al. 2005), speed (Shaywitz et al. 1998) as well as spelling and writing (Snowling 2000). Beginning readers usually use a letter-by-letter approach, i.e. they decode graphemes into phonemes, blend the phonemes to attain a phonological representation and subsequently retrieve the word meaning from memory (Ehri 1998). By gaining reading proficiency the visual word representations are stored in the orthographic lexicon and reading becomes an automated process.

1.3.2 Definition of developmental dyslexia

Dyslexia is a specific learning disability characterized by a significant impairment in reading skills despite normal intelligence (usually two standard deviations apart). Of all children with specific learning disabilities, over 80% have reading problems (Lerner 1989). A prevalence around 5% to 10% is assumed (Klicpera et al. 2007; Russeler et al. 2006; Schulte-Körne et al. 1998). The disorder can not be explained by age, visual problems or poor schooling (World Health Organization, 1993). Often reading comprehension skills and word recognition are also affected and spelling skills are reduced as well. Furthermore, visual confusions of letters as well as inversions and omissions are frequently encountered along with letter and/or syllable substitutions and additions. Inversions, omissions, letter and/or syllable substitutions as well as inconsistent errors despite training are also often observed in spelling (Habib 2000). Dyslexics often show poor reading accuracy and low speed, however reading accuracy depends on whether the language has a deep or shallow orthography, with regular orthographies relying more on fluency measures for diagnosing dyslexia (Wimmer et al. 2000). Languages with deep orthographies are

acquired more slowly compared to shallow orthographies (Gabrieli 2009) as the expression of phonological difficulty in dyslexics varies with respect to differences in written language (Ziegler and Goswami 2005). In cross-cultural studies however, it has been shown that across languages there is a similar rate of dyslexia, even though the relation of phonological processing to reading as well as the expression of dyslexics may vary across languages (Gabrieli 2009).

For children having a familial history of dyslexia the prevalence even ranges from 33% up to 50% (Gallagher et al. 2000; Pennington and Lefly 2001), indicating evidence of a genetic origin (Cardon et al. 1994; Galaburda et al. 2006).

An autosomal dominant inheritance has been supposed (Hallgren 1950) and several chromosomes and genes have been found to influence reading abilities. In twin studies a heritability of 70% for word reading has been proposed (Harlaar et al. 2005). In addition to research on the genetic origin, many theories assume that deficits in visual (Lovegrove et al. 1980; Stein and Walsh 1997), auditory (Baldeweg et al. 1999; Tallal 1980) or motor (Wolff et al. 1990) domains cause reading problems. However the phonological processing deficit hypothesis is the most accepted theory to date (Bradley and Bryant 1983; Ramus 2003) and is thus detailed in the next section.

1.3.2.1 The phonological deficit theory

A specific impairment in manipulating, storing and/or retrieving speech sounds has been supposed by the phonological deficit theory (Bradley and Bryant 1983; Ramus 2003). Learning to read requires the ability to map written graphemes (orthography) to their corresponding sounds (phonology), meaning that the conversion of graphemes to phonemes is crucial to reading acquisition (Frith 1995). Dyslexics often struggle already at this level of learning the letter-sound (Vellutino et al. 2004). The main problem in acquiring reading skills thus seems to be caused by a failure in the use of phonological representations of information (Goswami 2000). The phonological information processing problem becomes evident in rhyming tasks, for example, because compared to controls, dyslexics have more problems in rhyme detection due to their reduced phonological sensitivities (Bradley and Bryant 1983). Generally, three dimensions have been suggested to account for the phonological deficit: poor phonological awareness (Bradley and Bryant 1983; Liberman et al.

1974), poor phonological memory (Bowers and Kennedy 1993; Wolf and Bowers 2000) and reduced speed in rapid serial naming tasks (Snowling et al. 2000).
Phonological awareness is the sensitivity to the sound structure of language; the awareness that speech can be broken down into smaller units of sounds and conversely that smaller speech segments can be blended into syllables and words. It is the conscious ability to identify and manipulate the sound structure of words (Snowling 2000) and is one of the best predictors of later reading and spelling skills (Siok and Fletcher 2001). To acquire literacy, especially in alphabetic writing systems, a child's preliminary awareness of the sound structure of oral language is helpful for learning to spell and read (West and Stanovich 1986). Dyslexic children have difficulties or even miss developing such phonological awareness (Shaywitz and Shaywitz 2005). Even though dyslexics are not generally impaired in recognition memory and show average visuo-spatial memory skills, the phonological memory in dyslexics is poor (Everatt et al. 2006). Dyslexics specifically have difficulties in memorizing linguistic information such as syllables, words and sentences (Liberman et al. 1982), suggesting difficulties in storing verbal material (Kibby et al. 2004). Additionally, deficits in rapid naming are assumed to be due to deficits in automatization (Manis et al. 2000) thus rapid naming and access to the orthographic lexicon is reduced in dyslexics. Since access to verbal labels for visual stimuli (Logan 1988) such as letters, digits, objects and colours is poor, dyslexics have been found to be slower in naming compared to controls (Wolf and Bowers 2000).

1.3.2.1 Anatomical anomalies

Besides cortical malformations such as small neuronal aggregations (ectopias), loss of the characteristic cortical neuron organization (dysplasia) or even vascular malformations (Galaburda et al. 1985; Habib 2000), one of the most characteristic anatomical (post-mortem) findings in dyslexia is a symmetrical planum temporale (PT). This area is located on the supra-temporal surface, in the Sylvian fissure and posterior to Heschl's gyrus. During the course of language development the PT has been suggested to be an indicator for left hemispheric language lateralization because an asymmetry in volume (larger left hemispheric PT) can be found in normal readers but not in dyslexics (Galaburda et al. 1978). This relatively reduced PT in the left hemisphere for dyslexics has been related to poor verbal comprehension,

expressive language and phonological problems during reading (Larsen et al. 1990). These findings have been investigated with MRI technology, however MR studies could not verify previous results on the asymmetry in the PT and the findings were rather inconclusive (Shapleske et al. 1999). Also other structures have been identified to differ among normal and poor readers, for example a bilaterally shorter insula has been reported for dyslexics (Hynd et al. 1990). Posterior parietal areas especially in the right hemisphere have also been reported to differ by other investigators (Galaburda et al. 1978; Menghini et al. 2008). Furthermore, reduced grey matter volume has been observed bilaterally in the superior temporal gyrus, the anterior cerebellum, the right supramarginal gyrus and the fusiform gyrus as well as in frontal areas such as the pars triangularis of the inferior frontal gyrus (Middleton and Strick 1997; Paulesu et al. 2001; Ramus 2004; Steinbrink et al. 2008).

Not only grey matter, but also the white matter integrity and tracts have been compared between dyslexics and controls. With diffusion tensor imaging (DTI), the direction of water diffusion can be measured in the brain (anisotropy). The diffusion of water molecules diffusing along tightly packed fibres that go in one direction is highly anisotropic as the fibres are strongly directionally organized. An investigation of the relationship between reading ability and white matter tracts in children revealed that values of the fractional anisotropy in left temporo-parietal regions correlated with word identification skills (Niogi and McCandliss 2006). This means increasing reading skills are related to high white matter integrity in temporo-parietal areas, which correspond with the results of functional studies revealing reduced activity in these regions in poor readers (Shaywitz et al. 1998; Temple et al. 2001).

To summarize: in dyslexics specific areas belonging to the typical language network show anatomical anomalies or reduced grey matter and lower white matter integrity that may partly explain their reading difficulties. However, beside the anatomical findings there are also functional differences, which are reviewed in the following sections. It is still unclear whether those neural differences between normal and poor readers are the cause or the consequence of the disorder.

1.3.3 Visual word processing

Word recognition is one of the first steps in the reading process and therefore has been investigated frequently. Word recognition includes the access to stored

information through e.g. retrieving information about a word's spoken form and meaning from its printed form (Snowling 2005). Efforts to understand the processes involved in word recognition and reading have resulted in cognitive models. One of these models, the dual-route model of reading by Coltheart, is often used to explain reading disorders and the relevance of phonological awareness for beginning and skilled reading (Coltheart et al. 2001). It postulates that skilled readers access the meanings of frequent and familiar words directly (direct route or lexico-semantic route) but additional processing, such as letter-by-letter decoding and grapheme-phoneme conversion is necessary to read unfamiliar words and pseudowords. Children who learn to read mainly rely on the indirect route (or grapho-phonological pathway) and considerable phonological effort is needed to elaborate the phonological representation of words for lexical access (Katzir et al. 2005). Reading words includes phonological processes through grapheme-phoneme conversions, which are more important for young beginning readers than for adults. It is therefore highly interesting to examine young children at the beginning of reading acquisition when investigating phonological processes as the core deficit in reading development.

1.3.3.1 The N1 ERP - an indicator for print sensitivity

Neurophysiological studies have shown that specific visual areas specialize/sensitize for efficient print processing in the course of development and learning to read. Several ERP studies have reported word specific activation around 150-200ms (N1) after stimulus presentation at occipito-temporal sites, which tended to be left lateralized (Bentin et al. 1999; Brandeis et al. 1995; Brem et al. 2005). The N1 is the first component that differentiates between words and non-linguistic characters in readers (Bentin et al. 1999; Schendan et al. 1998; Tarkiainen et al. 1999). The N1 of non-reading children in kindergarten does not differentiate between symbols and words (even though letters might be more familiar to them) shown by similar amplitudes and topographical distributions to both conditions (Maurer et al. 2005). During acquisition of reading skills through a grapheme-phoneme association game (Graphogame) the initiation of print specialization was found in non-reading kindergarteners by an increase in the N1 sensitivity to words in both hemispheres (Brem et al. 2010). In normal reading 2nd graders the N1 print sensitivity is already well established and shows the characteristic left hemispheric lateralization of the

occipito-temporal negativity. The developing left lateralization is caused by neuronal reorganization after gaining experience in grapheme to phoneme mapping (Maurer et al. 2005; McCandliss and Noble 2003). Comparing adults with 2nd graders revealed a decreased N1 tuning in adults, which characterizes further reading practise. This points to a nonlinear development of neurophysiological specialization for print, with a maximum of tuning in young readers showing a high sensitivity to print compared to more selective tuning in adults (Maurer et al. 2006). In a follow-up study the reduced N1 amplitudes of poor reading at-risk children compared to control children pointed to a failure in automated processes in dyslexics (Regtvoort et al. 2006).
In conclusion, during acquisition of reading skills, print-specific activation seen in the N1 becomes increasingly left lateralized over occipito-temporal areas. This initial visual tuning for print seems to be deficient in dyslexics.

1.3.3.2 Print sensitivity in the visual word form system

During the emergence of print specialization in the left occipito-temporal region as found by the ERP studies, functional fMRI studies in parallel also showed the development of print specialization in the left inferior occipito-temporal area (Brem et al. 2010). Recent studies have demonstrated a posterior-to-anterior gradient of increasing print specificity in the basal occipito-temporal cortex referred to as visual word form system (VWFS) in adults and adolescents (Brem et al., 2006; Vinckier et al., 2007) as well as in children (Brem et al., 2009; van der Mark et al., 2009). Its centre is called visual word form area (VWFA) (Cohen et al. 2000). This region has been found to be dysfunctional in dyslexics as it showed an under activation in adult and adolescent dyslexics (Brunswick et al. 1999; Paulesu et al. 2001; Shaywitz et al. 2003) as well as in dyslexic children (Cao et al. 2006; Maurer et al. 2007; Shaywitz et al. 2002; van der Mark et al. 2009) in reading related tasks. Structural differences in grey-matter volume in five to six year old children at risk for dyslexia have been found in the left occipito-temporal cortex (Raschle et al. 2010).
Similar to the word specific left lateralized activity found on EEGs, fMRI studies have also revealed left hemispheric dominance during the development of reading. The typical left hemispheric dominance emerges in the language network already in 7-year old children (Balsamo et al. 2002; Gaillard et al. 2003), and this beginning lateralization increases into adolescence (Holland et al. 2001). The left lateralization

is associated with good reading skills in contrast to dyslexics who show a bilateral activation pattern (Pugh et al. 2000). The additional right hemispheric activity in dyslexics has been described as playing a role in compensation (Eden et al. 2004; Shaywitz et al. 2002).

In summary, corresponding to EEG findings, as well as in fMRI studies, the developing visual tuning for print could be detected by various studies, pointing to specific activity of the mid-fusiform gyrus (VWFA). Diminished activity was observed for dyslexics when compared to normal readers in this area.

1.3.4 Phonological processing impairments in dyslexia

Numerous studies have implicated phonological processing impairments as the core deficit in dyslexia (Ramus 2003; Torgesen et al. 1994). Therefore, investigating phonological processing in poor readers is very interesting. In addition to auditory tasks such as object naming or reading aloud words and pseudowords, typical visual paradigms to investigate phonological processes are rhyming tasks or pseudoword and pseudo-homophone reading tasks. Importantly, in visual rhyming tasks one has to consider the visually similar endings of rhyming words in shallow languages, indicating that investigations of phonological processes by rhyming tasks are not suitable for all languages.

1.3.4.1 Auditory and phonological processes

Early phonological processes have been detected around 320ms after visual stimulus presentation by Bentin and colleagues (Bentin et al. 1999). Non-pronounceable stimuli revealed a central, occipital positivity. Pronounceable stimuli showed two patterns in the topography: a negativity over left temporal regions and an occipito-parietal positivity. These early processes could be interpreted as pre-lexical processes of grapheme-phoneme-translations (Bentin et al. 1999). Further investigations have focussed on temporal auditory processing deficits, which have been described in dyslexics (Tallal 1980). By presenting deviant tones/phonemes among standard tones/phonemes in the background during an unrelated visual task, auditory processing and discrimination can been examined. This auditory paradigm is called the mismatch negativity task (MMN). The MMN activity generated in auditory

cortex peaks at fronto-central electrode sites with positive mismatch activity at the mastoids. This task provides an automatic event related potential to deviant auditory presentations (Näätänen et al. 2001). The early MMN occurs after 100-250ms and the late MMN after 300-600ms. The MMN is calculated as the difference of the ERP to rare deviant and frequent tones. It has been suggested that sources of sound features have their origin in the bilateral auditory cortex whereas speech sound deviances originate particularly in the left temporal area (Näätänen 2001). In particular the late MMN to phonemes has been reported to be attenuated in dyslexic children (Schulte-Körne et al. 1998). Younger children had longer latencies compared to older children and older children in turn had longer latencies than adults (Gomes et al. 1999; Gomot et al. 2000).

1.3.4.2 Regions involved in phonological processes

Imaging studies have reported activation in left-hemispheric brain regions including prefrontal and inferior frontal cortical areas (Booth et al. 2007; Cao et al. 2006) for phonological processes. Quite a few studies have examined whether activation in inferior frontal regions is related to good or poor language skills such as reading or rhyming, however the findings are inconsistent. While some studies found enhanced activity for dyslexics (Georgiewa et al. 2002; Rumsey et al. 1997; Shaywitz 1998; Temple et al. 2001) in frontal areas, others report the opposite with more activity in controls (Booth et al. 2007; Cao et al. 2006; Gross-Glenn et al. 1991; Paulesu et al. 1996). However, anterior regions are involved in phonological and articulatory processing and have been observed in silent reading and naming tasks (Fiez and Petersen 1998) as well. Phonological processing has also been described in other cortical areas including the superior temporal, the angular and supramarginal gyrus (Rumsey et al. 1997; Shaywitz and Shaywitz 2005). Further phonological activation has been found in middle and superior temporal areas for example for grapheme-phoneme decoding (Jobard et al. 2003; Price, Wise, Warburton et al. 1996; Rumsey et al. 1997; Sakurai et al. 2000) and sublexical speech perception (Turkeltaub and Coslett 2010). However, the attribution of specific processes to a certain brain area is rather difficult as most tasks not only test pure phonological processing but also involve semantic or lexical operations and vice versa. Therefore similar regions such

as the angular gyrus and the middle temporal gyrus have also been reported for semantic processing (Meyler et al. 2007; Shaywitz et al. 1998).

1.3.5 Prediction of dyslexia

To prevent poor reading children from the frustrations which often lead to depression, anxiety, inattentive and delinquent behaviour (Arnold et al. 2005), many investigators have tried to find behavioural (Manis et al. 2000; Puolakanaho et al. 2007), anatomical (Galaburda and Kemper 1979; Galaburda et al. 1985; Hynd et al. 1990; Semrud-Clikeman et al. 1996), electrophysiological (Guttorm et al. 2001; Maurer et al. 2009) or functional MRI markers (Hoeft et al. 2007) that contribute and improve prediction of reading outcome and dyslexia. Early prediction of dyslexia, ideally at preschool age, would allow targeted intervention and support before reading problems emerge and thus prevent negative school experiences.

1.3.5.1 Behavioural prediction of dyslexia

Besides the familial risk, behavioural measures at preschool or school age such as letter knowledge, phonological awareness, rapid naming and sentence imitation have been shown to predict future reading problems (Catts et al. 2001; Manis et al. 2000; Puolakanaho et al. 2007; Savage and Frederickson 2005). The advantages of using behavioural precursors of reading for prediction such as phonological awareness and other basic language skills are that these variables can be assessed quite early. For example, in 3.5 year old children the familial risk status together with rapid naming skills and letter knowledge predicted reading outcome (Puolakanaho et al. 2007). By the age of 4.5 years familial risk, phonological awareness and letter knowledge best predicted the reading disorder (Puolakanaho et al. 2007). Such behavioural data are able to provide good classification rates of e.g. 75% (Pennington and Lefly 2001) or even 93% (Catts et al. 2001). Altogether, there seem to be specific combinations of behavioural data at specific developmental stages providing an appropriate prediction of future reading (Puolakanaho et al. 2007).

1.3.5.2 ERP predictors from auditory processing

By investigating the activations evoked by the MMN task, reduced amplitudes in dyslexics were revealed in the late phoneme MMN, but not for the tone frequency deviances (Alonso-Bua et al. 2006; Schulte-Körne et al. 1998, 2001). Maurer and colleagues showed reduced amplitudes of the late MMN to subtle tone frequency deviance in children with a familial risk for dyslexia compared to control children in kindergarten. They further described that at-risk children showed a bilateral topography for the phoneme MMN in contrast to controls showing a more left-lateralized MMN. Together with behavioural data, especially the late MMN to phoneme deviances that indicated hemispheric lateralization enhanced the prediction for reading abilities in fifth grade correctly classifying 81% of the children at risk for dyslexia (Maurer et al. 2009). The late occurrence of the MMN effect has been related to an attentional re-orientation (Wetzel et al. 2006) or pre-attentive processing of sound change (Ceponiene et al. 2004) which might indicate deviant speech processes in dyslexics (Schulte-Körne et al. 1998). For early prediction based on auditory ERPs in newborns (Molfese 2000), three peak latencies from the left and right hemisphere as well as three amplitude measures from the right hemisphere were included and entered in a discriminant function analysis. The results yielded an impressive identification with 81% discrimination accuracy of 8-year old dyslexic, poor and normal readers (Molfese 2000). In another study, where consonant-vowel syllables were presented to newborns, it was shown that right hemispheric potentials at early and late latencies differentiated among children at risk for dyslexia and controls (Guttorm et al. 2001).

1.3.5.3 Functional and morphometric predictors

A correspondence of the familial risk for dyslexia and reduced grey matter was found in left occipito-temporal and bilateral parieto-temporal areas already in five to six-year old children (Raschle et al. 2010). In the visual rhyme judgement task in Hoeft et al. (2007) specific functional brain activation (right fusiform/middle occipital gyrus) and morphology revealed by voxel-based morphometry (VBM) of grey and white matter densities (grey matter: right anterior and posterior frontal gyrus; white matter: left inferior parietal lobule and left superior temporal lobule) in addition to behavioural

data at the beginning of a school year (children aged between 8 and 12 years) significantly enhanced the prediction of decoding ability at the end of that school year. These brain imaging measures yielded a model that explained 57% of the variance in later decoding abilities. The combination of behavioural data with neuroimaging measurements even explained 81% of the variance in the decoding ability (Hoeft et al. 2007). A classification of dyslexic children (6 to 16 years old) according to morphometric data of temporal and frontal regions (including six a priori selected morphometric brain measures: left and right length of the planum temporale, left and right length of the insula, left and right anterior width) was also reported (Semrud-Clikeman et al. 1996). Adding age and IQ to the anatomical predictors, they could enhance classification accuracy even more, from 60% to 87%.

To summarize, only a few studies have investigated predictability of reading outcome with functional or morphometrical MR data. The few existing studies clearly show the potential of combining behavioural and neuroimaging measurements for prediction as both ERP and MRI data significantly enhanced the explained variance in reading ability over behavioural data alone.

1.4 Conclusions, outline and hypotheses

An increasing interest in reading disorders has generated a large number of studies investigating reading skills with various imaging techniques in adults and children in terms of anatomical, behavioural, functional or genetic differences among normal and impaired or dyslexic readers. However, many theories on dyslexia are still being discussed and the causes remain unclear. Currently, agreement on the phonological impairment as a core deficit in dyslexia prevails. Several studies to date have investigated brain-related activity during phonological processing (which are largely implied in reading processes) to identify deficient activation patterns from childhood to adulthood. The results remain controversial, with investigators reporting enhanced or decreased activation in specific brain regions such as e.g. the inferior frontal gyrus. The identification of deficient areas or networks on the one hand aims at finding specific markers for early prediction of dyslexia, and on the other hand may provide targets for the development of specific, evaluated intervention programs. Targeted intervention programs are needed not only to improve reading, but also to prevent disappointment in school as well as the social, emotional and economic

consequences of the reading disorder (Meyler et al. 2008). The present PhD thesis contributes to a better understanding of phonological processing involved in reading acquisition of young children. It comprises two parts: (1) Demanding phonological processes in normal and poor 2nd grade readers were investigated and (2) Brain activation during processing of grapheme-phoneme transformations in kindergarten (i.e. before reading acquisition) was analysed in terms of its contribution for predicting poor and normal reading in the 2nd grade.

In Chapter 1 phonological processing was investigated and compared between good and normal 2nd graders using a new covert reading and mental letter substitution task. This task had been generated by adapting a subtest of a behavioural assessment for phonological skills (Basiskompetenzen für Lese-Rechtschreib-leistungen: BAKO) (Stock et al. 2003). This new task was designed because visual rhyming tasks are not suited for the German language. We used fMRI to examine whether activation and lateralization differences can be found between normal readers and their poor reading peers. Our task design with its phonological demands is suitable for investigating phonological abilities and their association with normal and poor reading skills. As a dependency between phonological and reading skills has consistently been reported, we assumed that in our study measurements of phonological awareness would be closely related to reading skills in the 2nd grade. Furthermore, because poor readers have reduced sensitivities in phonological processing, by comparing normal and poor readers we assume to reveal differences in brain activation.

In Chapter 2 we investigated the potential of neuroimaging measures in kindergarten for prediction of reading skills in the 2nd grade. The children took part in a longitudinal study and participated in a grapheme-phoneme association training. Neuroimaging data of the children were assessed in kindergarten, before and after training as well as in 2nd grade. We used neuroimaging measures from an explicit visual word processing task after the training in kindergarten for prediction because by then the children had already learned the basics of print decoding (or reading). Explicit word processing after training yielded a print sensitive response of around 188ms-281ms after presentation of the words as shown in the ERP. Corresponding to the print sensitive activation seen in the ERP and based on previous findings of print sensitive

activation in the VWFA, fMRI activation of the left midfusiform gyrus was chosen as a predictor. We hypothesized that combining specific behavioural measures with the print sensitive responses recorded in the EEG and fMRI (Brem et al. 2010) improves discrimination of poor and normal readers in the 2nd grade.

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2 EARLY EMERGENCE OF DEVIANT FRONTAL FMRI ACTIVITY FOR PHONOLOGICAL PROCESSES IN POOR BEGINNING READERS *

2.1 Abstract

Phonological awareness refers to the ability to perceive and manipulate the sound structure of language and is especially important when children learn to read. Poor phonological awareness is considered the major cause for the emergence of reading difficulties. In this functional magnetic resonance imaging (fMRI) study we examined the brain correlates of phonological processing in young beginning readers (aged 8.3±0.4y, 2nd grade) with poor (<25th percentile) or normal, age-appropriate reading skills (>40th percentile) using a covert reading and mental letter substitution task. Letter substitution in words and nonwords induced pronounced activity in a left frontal language network related to phonological processing, with maxima in the left inferior frontal gyrus and in the insula. The activation within this frontal network increased with better reading skills and differentiated between normal and poor reading young children. Lateralization indices of overall frontal activity for normal and poor readers pointed to stronger left hemispheric involvement in normal readers as compared to the more bilateral activation pattern in poor readers.

To summarize, young children with age-appropriate reading skills display a left hemispheric dominance characteristic for language processing already by grade two. The more bilateral activation pattern in poor readers points to an increased effort and the emergence of compensatory strategies for reading and phonological processing just 1.5 years after the start of formal reading instruction.

2.2 Introduction

Poor reading skills represent a major problem in our modern society and are responsible for many troublesome school careers and cause considerable social costs. About 5% of the schoolchildren are diagnosed with developmental dyslexia, a

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specific reading disorder. For reading acquisition in alphabetic writing systems, preliminary awareness of the sound structure of oral language is beneficial (Bradley and Bryant 1983; West and Stanovich 1986). Children with dyslexia have difficulties or even miss to develop phonological awareness (Shaywitz and Shaywitz 2005; Wagner and Torgesen 1987; Wagner et al. 1997). They often struggle from the very start when learning the alphabetic principles that involve knowledge of grapheme-phoneme correspondences, which initialize the emergence of print sensitive brain networks (Brem et al. 2010) and, in turn, critically affect reading accuracy and speed as well as spelling and writing (Ehri 1998; Snowling 2000).

Cognitive reading models such as the dual-route model of reading (Coltheart et al. 2001) are useful in explaining reading disorders (Snowling 2005) and the relevance of phonological awareness for beginning and skilled reading. Children who learn to read usually rely on the indirect route to read words as they first decode words on a letter-by-letter approach by translating graphemes into phonemes and subsequent phoneme blending. They thus need considerable phonological effort to attain the phonological representation of words for lexical access (Ehri 1998), thereby also explaining the dependency of phonological and reading skills.

Functional imaging studies on phonological processing reported activation in different subsystems of the reading system (Richlan et al. 2009; Sandak et al. 2004) such as the the left hemispheric brain regions including inferior frontal cortical areas (Bles and Jansma 2008; Booth et al. 2007; Cao et al. 2006; Hoeft et al. 2006; Shaywitz and Shaywitz 2005) in tasks involving effortful selection, retrieval or manipulation of phonological representations (Fiebach et al. 2002; Fiez et al. 1999), subvocal articulatory rehearsal (Smith and Jonides 1998), or the pronounceability of print (Frost et al. 2009). Also, temporoparietal regions including the superior temporal, supramarginal and angular gyri as well as occipito-temporal areas have been associated with phonological processes (Church et al. 2008; Paulesu et al. 1993; Pugh et al. 1996; Rumsey et al. 1997; Shaywitz and Shaywitz 2005). Within these different subsystems deviant activity in the form of under- or overactivation during reading and e.g. phonological processes has been shown in dyslexic as compared to normal readers as summarized in a recent meta-analysis (Richlan et al. 2009). In the frontal cortex, phonological processing most often has been attributed to the activity in the posterior and dorsal part of the inferior frontal gyrus and along the precentral gyrus (Jobard et al. 2003; Poldrack et al. 1999; Vigneau et al. 2006), and this frontal

activity differed between normal and poor readers. Some studies on reading and rhyming in adults found more left inferior frontal activation for those with dyslexia than for controls (Brunswick et al. 1999; Rumsey et al. 1997; Shaywitz et al. 1998), but others reported more activation for controls (Gross-Glenn et al. 1991; Paulesu et al. 1996). Also for children the results are rather inconsistent with dyslexia leading to either more (Georgiewa et al. 2002; Temple et al. 2001) or less activation in the inferior frontal gyrus (Bolger, Minas et al. 2008; Booth et al. 2007; Booth et al. 2008; Cao et al. 2006; Georgiewa et al. 1999; Shaywitz et al. 2002). The meta-analyses by Richlan et al. summarized the local activation differences between good and poor readers in the left inferior frontal gyrus with more pronounced activity in the anterior insula and primary motor cortex close to the mouth area and underactivation in the opercular part of the inferior frontal gyrus in poor readers. Overactivation in poor readers is usually explained by increased effort and the involvement of additional resources or compensatory processes for reading (Richlan et al. 2009). Less activity in the reading network of impaired readers including the inferior frontal gyrus directly shows deficient processes such as ineffective integration of orthographic and phonological information (Bolger, Minas et al. 2008) or dysfunctional access to lexical and sublexical phonological representations (Richlan et al. 2009). Whether or not young normal developing readers in 2nd grade already show activation differences to peers with poor reading skills in the form of over- or underactivations in specific brain regions will be examined in the present study.

Not only left frontal activity has been a matter of debate in normal and poor readers, but also differences in hemispheric activity patterns have been discussed and partially quantified by reporting lateralization indices (LI) (Gaillard et al. 2003; Gaillard et al. 2000; Wilke and Schmithorst 2006; Yuan et al. 2006). The typical left hemispheric dominance in the language networks emerges very early in childhood and has been shown in 7-year-old children already (Balsamo et al. 2002; Gaillard et al. 2003). This lateralization further increases to adolescence as shown in a verbal fluency task (Holland et al. 2001). The left lateralization not only changes in development but is also correlated with reading skills, as shown by the increase in activation of left inferior frontal regions in adults (Pernet et al. 2009) and by a more bilateral activation pattern found with dyslexia (Pugh et al. 2000). The right hemispheric activation in poor reading adolescents and adults has usually been interpreted in terms of compensation (Eden et al. 2004; Shaywitz et al. 2002). But

whether the reading network of young poor reading children already differs in the lateralization from normal reading peers, which would indicate alternative or even emerging compensatory processing strategies to overcome phonological deficits still has to be clarified.

To examine phonological processing, auditory (Booth et al. 2007), visual word (Bolger, Minas et al. 2008; Cao et al. 2006; Hoeft et al. 2006) or letter rhyming tasks (Paulesu et al. 1996; Shaywitz et al. 1998; Temple et al. 2003) have typically been used. In German visual rhyming tasks, rhyming word pairs usually have an increased visual similarity compared to nonrhyming pairs, with the consequence that pure visual matching strategies allow to solve rhyming tasks, without phonological processing. Other paradigms used to study phonological processes are word vs. pseudoword and/or pseudohomophone reading (Kronbichler et al. 2007; Miellet and Sparrow 2004; van der Mark et al. 2009). Yet, poor beginning readers may have difficulties to distinguish between words and pseudohomophones due to the lack of orthographic knowledge. To overcome these problems, we used a covert reading and mental letter substitution task suited to track the activation pattern in 8-year-old age-appropriate and poor beginning readers in 2nd grade. This task involved reading words or pseudowords followed by the mental substitution of a letter and a final lexical decision. The control condition, similar to the substitution condition involved reading and memorizing words and pseudowords as well as lexical decisions but no active manipulation of the sound structure of the memorized word or pseudoword was required. The contrast of the two conditions thereby accentuate phonological processing in our children with little reading experience and minimize other processes such as lexical decisions or working memory involvement.

Taken together, despite growing knowledge about phonological processing and the reading network in children and adults, little is known about brain processes at the very beginning of reading acquisition, when the problems of dyslexic children start to emerge. The present study therefore examines neural and functional differences presumably before less efficient reading strategies of poor readers are consolidated.

2.3 Materials and methods

2.3.1 Study design and subjects

Fifty-two healthy, right-handed native (Swiss-) German-speaking 2nd grade children participated in this study, which included a behavioural test battery, electro-encephalography (EEG), and functional magnetic resonance imaging (fMRI) recordings in separate sessions. The data of 17 children were excluded from analyses due to either poor task performance (accuracy < 65%, n=11), excessive movement during the fMRI scan (translation/rotation: >2mm/2°, n=4), developmental speech disorder (n=1) or problems with attention (n=1) according to the Child Behaviour Checklist CBCL (Achenbach 1991) completed by the parents. The remaining 35 children (mean age 8.3 ± 0.4 years; 21 girls) all reported normal or corrected-to-normal vision and had an estimated IQ of ≥85 (block design test of the HAWIK-III) (Tewes, et al. 1999). The children (n=35) were grouped into normal, age-appropriate (NR; >40th percentile; n=18, mean age 8.3 ± 0.4; 11 girls) (Manis et al. 1996; Shaywitz et al. 2003) or poor readers (PR; <25th percentile; n=14, mean age 8.3 ± 0.3; 7 girls) (Rutherford 2006; Shaywitz et al. 2002) according to their reading performance (number of correctly read words per minute, subtest of Salzburger Lesetest: SLT) (Landerl et al., 1997). The three remaining children had reading scores between the 25th and the 40th percentile (gap group, 2 girls) and were only included in regression analyses. The 11 children that were excluded on the basis of poor performance in the fMRI task belonged to all three reading performance groups (NR n=6, PR n=4, and gap groups n=1) and did not show clinical or subclinical attentional problems according to the CBCL. Informed consent for participation in the study was given by one parent/caretaker of the child and the children gave assent. The study was approved by the local ethics commission. Children received a book voucher of CHF 50 for participation in the study.

2.3.2 Task

The covert reading and mental letter substitution task performed in the MR scanner is illustrated in Fig. 1. German words or pseudowords consisting of four capital letters (graphemes), with one of its letters (first or last) marked in red, were presented for

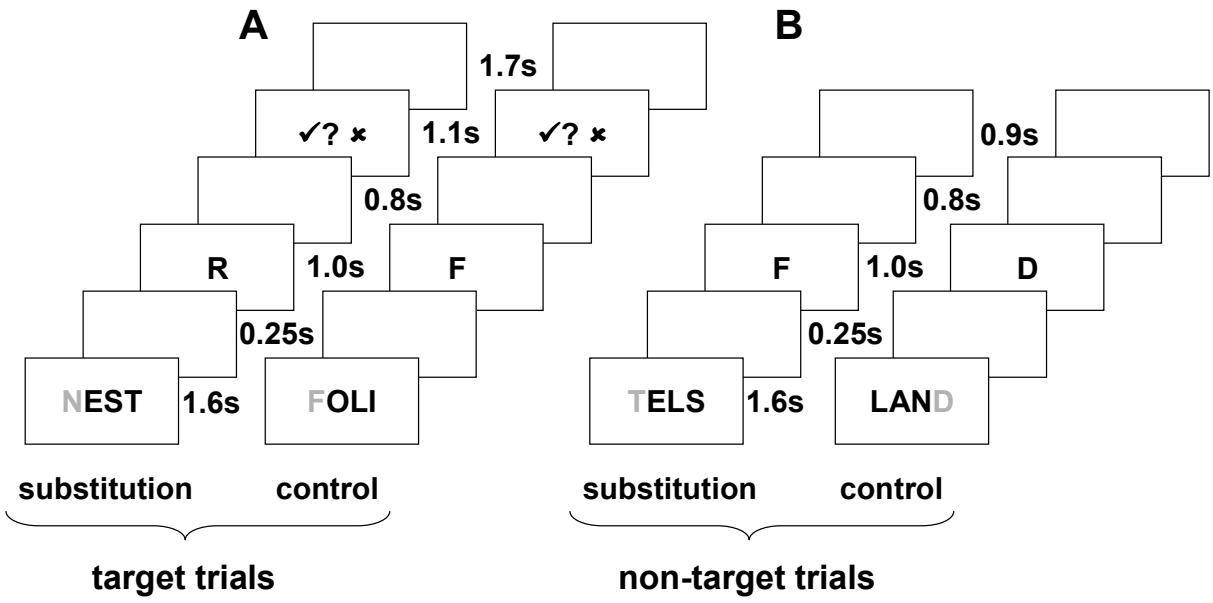

Figure 1:
Task procedure: A) A substitution target trial is shown on the left, a control target trial is shown on the right. Note: only in 20% of the trials a question mark appeared (=target trial). Only in these trials, children were required to decide by button press on the lexical status of the newly formed word/pseudoword. B) A substitution trial is shown on the left, a control trial is shown on the right. In non-target trials only a mental decision and no motor response was required.

1.6 seconds. The marked letter then had to be mentally replaced by a subsequently presented single letter. Subjects then performed a lexical decision and decided whether or not the newly formed (generated) letter string referred to a real word (W) or a pseudoword (Pw). The regular orthography in German allowed letter-by-letter* reading, and therefore, the words had not to be read as a whole in order of getting a phonological correct representation. There were two different types of trials: In the substitution condition S, children had to mentally replace a letter of a W or Pw resulting in a different W (SW; generating new words, W-W: **N**EST *(*English *nest)* – R – *rest (*English *rest),* Pw-W: **T**ELS – F – *fels (*English *cliff*)) or Pw (SPw; generating new pseudowords, Pw-Pw: HAP**O** – E – *hape*, W-Pw: HAS**E** *(*English *rabbit*) – U – *hasu*). In the control condition C the letter marked in the W or Pw had to be replaced by the very same letter, requiring no further mental phonological manipulation or letter substitution. The two control trial types included words (CW; W-W: LAN**D** *(engl. land)* – D – *land)* and pseudowords (CPw; Pw-Pw: **F**OLI – F – *foli*). The position of the letter to replace (always first or last letter in a W, Pw), word frequency

* Only few words and pseudowords (8 S, 8 C) included also complex graphemes or diphthongs consisting of two letters (e.g. ch, au, ei). However, in those items the two letters forming the complex grapheme/diphthong were never changed by a manipulation (substitution of a letter) and therefore always represented the same sounds across the whole trial.

(http://wortschatz.uni-leipzig.de/: substitution 395±2.3; control 416±2.3; *p*=0.327), bigram-frequency (sum of the number of occurrences of each bigram of a W, Pw in the CELEX database; substitution 700746±5326; control 694203±5118, *p*=0.920) (Baayen et al. 1993) and word type (verb, noun) were balanced between the conditions. A total of 112 trials were presented (56 substitutions, 56 controls). Target trials (20%, half substitution and half control trials) were followed by a question mark flanked by the response options. There, children decided by button press with middle and index finger of their dominant hand, whether the newly generated letter string was a word ("✓" button) or a pseudoword ("x" button). The assignment of the response buttons to the word-pseudoword judgment in the target trials was counterbalanced across subjects (15 children right button for word/ 20 children right button for pseudoword and vice versa: the slight overrepresentation of the assignment "pseudoword right"/ "word left" resulted from the exclusion of 17 children). The children were instructed to mentally substitute the marked letter in every single trial as soon as the letter was presented because there was not enough time for the response if they waited for the question mark. To allow for event-related modelling 66 null events were randomly intermixed within the trials.

Given that the task required word and pseudoword reading as well as substitution of letters, especially for PR the task was quite difficult. To ensure that the analyses included only children who were able to perform the task with moderate to good performance, children with a total performance below 65% in both conditions were excluded. Because of the high number of children with poor task performance (n=11), we have repeated the core analyses also for an enlarged group of 46 children by including those children with poor task performance. The results of the enlarged group are summarized in the Supplementary material online (A) and converged with our core results.

2.3.3 Behavioural assessment and statistics

Before the imaging sessions an assessment of reading and writing skills (Landerl et al. 1997) phonological skills ("Basiskompetenzen für Lese-Rechtschreibleistungen BAKO": the total score included seven subtests: pseudoword segmentation, vowel substitution, rest word identification, phoneme inversion, sound categorization, vowel length determination and word inversion) (Stock et al. 2003), working memory

(adapted digit span forward and backward by repeating colour names with behalf of a visual template), rapid naming (RAN) and estimated verbal and nonverbal IQ (HAWIK-III: Hamburg-Wechsler-Intelligenztest für Kinder; subtests block design (non-verbal) and similarities (verbal)) (Tewes et al. 1999) were conducted at the children's home. In this assessment, all words and pseudowords used in the experiment were read and classified by the children as existing or non-existing to make sure the children were familiar with the words and were able to identify the pseudowords. Whenever a word/pseudoword was misclassified, they were explained to the children. Further the two methods (EEG and fMRI) were explained to the children with pictures to prepare them for the imaging sessions. Parents rated the child's behavioral problems and competencies by the CBCL questionnaire (Achenbach 1991).

Group differences between NR and PR were assessed with independent t-tests for age, attentional scores, estimated verbal and nonverbal IQ, working memory, rapid naming, phonological skills (total score BAKO, measure in percentile), reading (SLT: correct words per minute, measure in percentile) and writing scores.

For the covert reading and mental letter substitution task, we analysed the accuracy and reaction time on correct targets and compared in scanner performance between conditions (substitution and control) and groups (NR and PR). A multivariate analysis of variance (MANOVA) was calculated for accuracy and reaction time separately with factors condition and group. Posthoc t-tests were used when necessary to explain MANOVA results.

2.3.4 FMRI recordings, processing and analysis

Functional imaging data was acquired on a 3-T (GE Medical Systems) scanner in the Children's Hospital in Zurich using a T2*-sensitive ultrafast multislice echo planar imaging (EPI) sequence sensitive to blood oxygen level-dependent (BOLD) contrast. In the fMRI sessions, particular care was taken to stabilize the children using custom-made padding and fixations. Children wore earplugs and headphones and a noise insulation mat was used to protect from scanner noise. Visual stimulation was accomplished with MR compatible TFT video goggles. The whole scanning session lasted for about 2.5h, including the scanning procedure demonstration with a teddy bear, an audiovisual word and false font processing task and a simple reading task

not being described here. Children took at least one break outside the scanner in between the different tasks. The order of the three tasks was counterbalanced across subjects so that the covert reading and mental letter substitution task was at the beginning of the scanning session for 9 children, at the end for 10 children and in the middle for 16 children. The slight inconsistency in balancing resulted from several exclusions. But a supplemental MANOVA for task performance (accuracy for substitution, control) in which children were grouped according to the order of the tasks in the scanning session (task order: start, middle, last) revealed no main effect of task order (neither for the whole group ($F(2,32)=2.16$, $p=0.13$) nor for the separate groups of PR ($p=0.586$), NR (trend $p=0.056$)). Because of the lack of major performance differences with task order, no further analyses were conducted.

Recordings of 442 volumes were conducted (32 axial slices, TR = 1700ms, TE = 31, matrix 64x64, voxel size=3.44 x 3.44 x 3.8 mm^3, flip angle 70°, FOV=220mm^2). To exclude T1 saturation effects the first 4 volumes were excluded from analysis.

SPM5 software (Wellcome Department of Cognitive Neurology, London, http://www.fil.ucl.ac.uk/spm) was used for image processing and statistical analysis. Standard processing steps included slice-scan-time correction, realignment, normalization of the images using a 7th-degree spline interpolation method to match to the Montreal Neurological Institute template (MNI) as in other studies with children (Beaulieu et al. 2005; Bolger, Hornickel et al. 2008; Kucian et al. 2006; Schulz et al. 2008; van der Mark et al. 2009), resampling to isometric voxels (3 mm^3) and smoothing with a 9mm full-width at half maximum isotropic Gaussian kernel. Although transforming children's brains to an adult standard atlas may introduce some shape and variability differences in specific locations, these differences do not substantially affect functional imaging data, especially in children older than 7 years of age (Burgund et al. 2002; Kang et al. 2003).

The event-related activation was filtered with a 128-s high-pass filter and modelled with the standard SPM hemodynamic response function. Serial correlations were accounted for using an autoregressive model of the first order. In the subject-specific first-level model, the event-related activation to the onsets of the presented single letters (which determined the type of subsequent processing) for each of the four different trial types (SW, SPw, CW, and CPw) were modelled separately as events of interest. Further, also the onset of the target (T) question mark and the onsets of the initial word/pseudoword were also included in the design matrix as events of no

interest, resulting in nine regressors (see design matrix in Figure B of the supplementary data). The analysis focused on the brain activation related to the mental substitution of a letter in a memorized word/pseudoword. Therefore only the activation related to the onset of the single letters for either substitution (S: SW, SPw) or control (C: CW, CPw) trials was further investigated and compared.

2.3.5 Brain activity pattern underlying letter substitution

Whole brain voxelwise analyses: Statistical parametric contrast maps of t-values (SPM t-maps) were generated by computing the averaged intensity of voxels in the t-statistics. All statistical thresholds reported are corrected for multiple comparisons (p<0.05) using a cluster extent threshold. To enforce an a priori corrected threshold of p<0.05 we used the Monte Carlo simulations procedure in MATLAB as detailed in articles by Slotnick (Slotnick et al. 2003; Slotnick and Schacter 2004). This procedure models the whole functional image volume and takes into account the 3-dimensional smoothing kernel (9mm^3) and an assumed type I error voxel activation probability (i.e. p<0.005 for the regression and group contrasts, p<0.0005 for the condition contrasts). After performing 10'000 simulations, the cluster extents that yielded a p<0.05 for the assumed p-values (p<0.0005, k=15 and p<0.005, k=24were selected for use in cluster extent thresholding.

We report the results of 2nd-level random effect analyses based on the individual contrast images to characterize the activation evoked by each condition (vs. rest) and the condition difference for the whole sample and for each subgroup separately (Fig. 2).

Two-sample t-tests were used to determine group differences for each condition and the condition contrast (substitution vs. control). In addition, the contrast images of substitution versus control trials were correlated with the children's reading scores. Activated brain structures were identified by transforming the MNI coordinate system of SPM5 into the standard brain atlas of Talairach and Tournoux, 1988 and using the Talairach Daemon (Lancaster et al. 2000).

2.3.6 Region of interest analyses

Three local maxima in the inferior frontal network (including 2106 voxels; insula INS: x=-33, y=21, z=12, anterior inferior frontal gyrus aIFG: MNI coordinates x=-45, y=30, z=15 and posterior inferior frontal gyrus pIFG: MNI coordinates x=-51, y=9, z=24) showing more pronounced activation to substitution than control trials were chosen for a posthoc region of interest analyses (spherical ROIs, radius=8mm). The mean percent signal change of these ROIs and their right hemispheric homologues were extracted on unsmoothed images (MarsBar version 0.41) (Brett et al. 2002). To characterize the condition main effect revealed by the whole brain analysis and its modulation by group, 2x2 MANOVAs (group x condition) were calculated for each left hemispheric ROI and posthoc t-test were used to clarify the interactions. Condition main effects of these MANOVAs are not discussed and the ROIs of the left and right hemispheres were not introduced in the same analyses as statements about condition main effects and about laterality would have been strongly biased by ROI selection (Kriegeskorte et al. 2009). But correlations with the reading and the phonological score were computed for the left and right hemispheric ROIs of the aIFG, pIFG and INS. A posthoc correlation of digit span with the ROIs of the condition difference clarified the influence of working memory processes.
In addition to the functionally defined centres of the ROIs INS, aIFG and pIFG we also defined two literature-based spherical ROIs. The centres of the additional two ROIs (r=6mm to avoid an overlap) based on the recent meta-analyses by Richlan et al. (2009) and included two brain areas in the left inferior frontal cortex with either reported underactivation (opercular part of the IFG x=-46, y=16, z=6 referred to as ROI “opIFG”) or overactivation (anterior insula x=-34, y=18, z=-4, referred to as “aINS”) in dyslexics as compared to normal readers. To examine ROI, group and condition differences, the two ROIs were included in a 2x2x2 MANOVA with between-subject factor group and within-subject factors condition and ROI (opIFG, aINS).

2.3.7 Lateralization index

We were also interested in hemispheric differences in the frontal activation between groups and its relation to children’s reading skills. The pickatlas from the SPM

toolbox (Maldijan et al. 2003) was used to anatomically define a mask of the left and right frontal lobes. Afterwards the number of activated voxels for each condition vs. baseline within the left and right frontal lobes exceeding a threshold of $p<0.001$ (uncorrected) was determined for all children. The lateralization index (LI) was then calculated for each subject separately by subtracting the number of frontally activated voxels on the right side from the activated voxels on the left side and then dividing the result by the sum of frontally activated voxels of the left and right side (LI = (L-R) / (L+R)) (Holland et al. 2001). The LI was calculated for each group and the group difference in LI was examined with an independent t-test. A correlation of the LI with the reading score for both conditions was calculated as well. Lateralization indices between 0.20 and -0.20 represent bilateral activation (Binder et al. 1996; Gaillard et al. 2002; Gaillard et al. 2003). We further used the number of activated voxels of either condition to determine lateralization differences between groups and conditions with a 2x2x2 MANOVA (condition x hemisphere x group). Posthoc paired and independent t-tests were used when necessary to explain MANOVA results.

A series of correlations between behavioural and fMRI (ROI, LI) measures were computed to characterise the results. Because of the problem of reporting false-positives when conducting multiple tests we have marked those correlations that survive the stringent Bonferroni correction ($p<0.002$) with an asterisk (*).

2.4. Results

2.4.1 Behavioural data

In the full sample (n=35), children's reading and phonological scores were highly correlated ($p=0.001$*, r=0.520; Fig. 3A). PR and NR did not differ in age, attentional scores given by the CBCL, nonverbal IQ, or digit span but PR performed significantly worse on the verbal IQ, the rapid naming task, the phonological screening test, the reading test, and the writing test (Table 1).

Overall in-scanner task performance in the covert reading and mental letter substitution task of the fMRI session was high (mean ± SD: substitution 81.2± 9.8%, control 86.0±11.2%, see Table 2a). The MANOVA for accuracy with between-subject factor group (NR and PR) and within subject factor condition (control and substitution) showed a trend for the main effect of condition ($F(1,30)=4.1$, $p=0.053$),

Table 1:
Group comparison for demographics and behavioral tests

	NR (n=18) Mean ± SD	**PR (n=14)** Mean ± SD	***P***
Pretest age (years)	8.3±0.4	8.3±0.3	*0.765*
Attention score (CBCL)	46.3±7.1	51.5±9.1	*0.118*
Nonverbal-IQ (block test)	114.2±11.4	108.9±14.3	*0.258*
Verbal-IQ (similarities)	125.3±13.7	111.8±13.5	***0.009***
Digit span forward	6.1±1.9	5.4±1.3	*0.297*
Digit span backward	4.2±1.4	4.1±1.1	*0.840*
Rapid naming (speed in seconds)	30.0±5.4	34.1±4.1	***0.027***
Phonological score (BAKO; total score, percentile)	48.2±20.1	32.3±16.6	***0.024***
Reading score (SLT; words per minute, percentile)	71.4±19.7	10.5±8.4	***<0.001***
Writing score (SRT; ortho-graphic errors)	6.7±3.3	11.6±2.7	***<0.001***

Table 2a:
Overall in-scanner task performance by condition

All children (n= 38)	**Substitution** Mean ± SD	**Control** Mean ± SD	***P***
Accuracy (% correct)	81.2±9.8	86.0±11.2	***0.031***
Reaction time (ms)	2838.0±253.1	2910.2±560.6	*0.391*

Table 2b:
Group comparisons of in-scanner task performance by condition

Accuracy (% correct)	**NR (n=18)** Mean ± SD	**PR (n=14)** Mean ± SD	***P (groups)***
Substitution	83.3±11.1	78.0±8.4	*0.143*
Control	87.5±11.9	83.3±11.3	*0.323*
P (conditions)	*0.226*	*0.120*	
Reaction time (ms)	**NR (n=18)** Mean ± SD	**PR (n=14)** Mean ± SD	***P (groups)***
Substitution	2787.3±230.5	2872.6±245.3	*0.321*
Control	2814.1±283.2	3033.1±811.4	*0.294*
P (conditions)	*0.423*	*0.449*	

and a post hoc t-test (p=0.031) indicated that the control trials were responded more accurately than the substitution trials. NR and PR performed similarly for both conditions. No differences were found for reaction times, neither between groups nor between conditions (Table 2b). The absence of any differences in the reaction time

has to be interpreted with care as children were asked to make their lexical decisions in their minds before the question mark was shown. Both reading (p=0.041, r=0.347) and phonological scores (p=0.004, r=0.475) significantly correlated with in-scanner task performance.

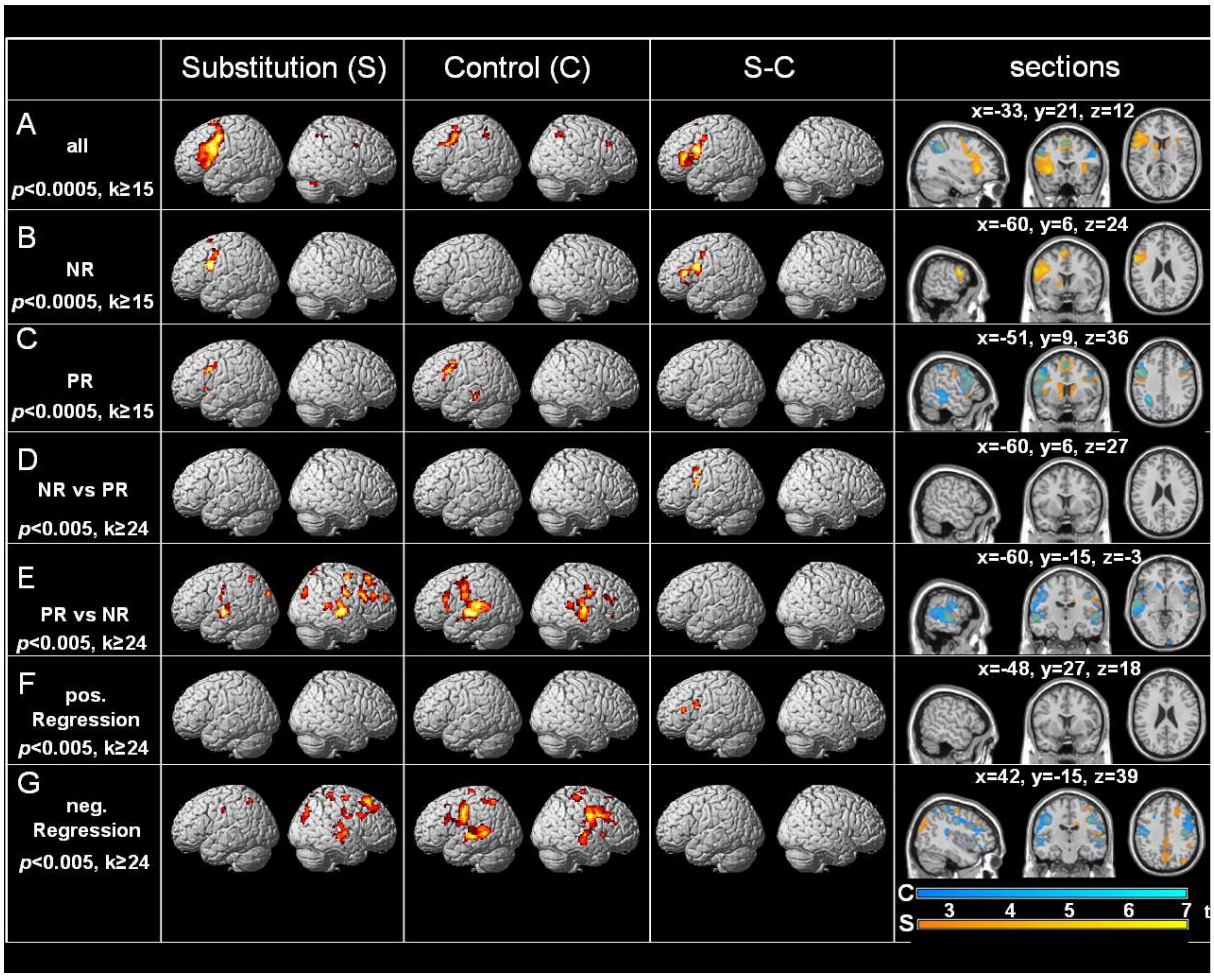

Figure 2:
Condition versus baseline contrasts for S (first) and C (second) and their difference (S-C: third row) at cluster-extent corrected thresholds (A-C: p<0.0005, k≥15 and D-G: p<0.005, k≥24) are illustrated. In the section view on the right the activation detected for S (yellow-orange) and for C (blue) are overlaid on sagittal, coronal and axial slices for t ≥ 2.5. A) The condition difference (substitution vs. control) for the whole sample (n=35) revealed more activation in the superior and middle frontal gyrus, the insula (INS) as well as the inferior frontal gyrus (aIFG and pIFG) for the substitution condition. (B) The condition difference (substitution vs. control) for the normal readers (n=18) revealed more activation in the inferior frontal gyrus and precentral gyrus. (C) No activation difference was detected between substitution and control trials in poor readers (n=14). (D) Normal readers exhibited more pronounced activation for the main condition contrast (S>C) as compared to poor (n=14) readers in the middle and inferior frontal gyrus. (E) No brain area showed increased activation for the condition difference in poor readers (n=18), but an extended network showed more pronounced activity in PR when looking at S or C vs. baseline. (F) The positive correlation of the condition difference with the reading score indicated an activation increase with better reading skills in the inferior frontal gyrus and the insula. (G) The negative correlation of the condition difference with the reading score showed the absence of brain areas that are specifically activated in children with poor reading skills. Note, when looking at the negative correlations of each condition with reading score, an extended frontotemporal network is related to poor reading skills (see also panel E).

2.4.2 FMRI results

Condition difference. For the whole sample of 35 children the left superior frontal gyrus, middle frontal gyrus, insula and inferior frontal gyrus displayed more pronounced activation to substitution vs. control trials (Fig. 2A and Table 3A). When looking at the condition differences for NR (Fig. 2B and Table 3B) and PR (Fig. 2C and Table 3C) separately, only NR exhibited more pronounced activation for substitution than control trials in the left frontal cortex, even when lowering the threshold to $p<0.005$, k=24 (Fig. 2B). The absence of any condition difference in PR can be explained by the very similar activation pattern seen in PR for substitution and control conditions (Fig. 2C) as compared to NR with clearly more pronounced activation for the substitution condition in a left frontal network (Fig. 2B).

Group comparison. The group comparison for the difference of substitution vs. control trials revealed more activation for NR in the inferior frontal gyrus and the middle frontal gyrus (Fig. 2D and Table 3D). PR did not show any region with more pronounced activity for the condition difference as compared to NR but PR exhibited more pronounced activation in a bilateral fronto-temporal network when looking at the substitution and the control conditions separately (Fig. 2E and Table 3E).

Brain activity and reading skills. A voxel-based regression analysis of the condition difference with the reading score for all 35 children was computed to study the relationship between reading skills and fMRI activity. This analysis revealed a positive correlation of fMRI activity with the reading score (Fig. 2F and Table 3F) in the inferior frontal gyrus and in the insula, showing that better reading skills were associated with more pronounced activation for S than C in these regions, although task completion for both the substitution and control conditions evoked more activity in frontal, temporal, and parietal regions the poorer the reading skills of the children (Fig. 2G and Table 3G).

An overview of activation patterns is given in Fig. 2 A-G and Table 3. The main condition contrasts are also summarized for the whole sample (including the 11 children with poor task performance) in the Supplementary material online (A). The results of the additional analyses are in line with the results of the main text.

2.4.3 Region of interest analyses

ROIs in INS, aIFG and pIFG. Three local maxima in the left inferior frontal network revealed more pronounced activation to substitution than control trials over the whole sample (Fig. 2A). The spherical ROIs with their centres at these local maxima were subjected to three separate 2x2 MANOVAs to detect group differences and interactions between groups and conditions. No main effects for group were found in any of the three ROIs, but the left aIFG and pIFG ROIs pointed to an interaction of condition and group which was explained by more pronounced condition differences in NR compared to PR (aIFG: $F(1,30)=6.8$, $p=0.014$; pIFG: $F(1,30)=6.6$, $p=0.016$; Fig. 4 and Table 4).

The reading scores correlated with the activity of the condition difference in the left aIFG ($p=0.004$, r=0.472) and pIFG ($p=0.012$, r=0.437; Fig. 3B). The activation difference between S and C in the right hemispheric homologue of the pIFG tended to correlate with the phonological score ($p=0.078$, r=0.316) and when the reading score was partialled out the correlation reached significance ($p=0.025$, r=0.402). This partial correlation remained significant in the group of poor readers only ($p=0.017$, r=0.646; Fig. 3C). No significant correlation was found for the digit span with the condition difference.

Literature-based ROIs in the left opercular IFG (opIFG) and the left anterior INS (aINS) (Richlan et al. 2009): The 2x2x2 MANOVA with between-subject factor group and within-subject factors ROI (opIFG and aINS) and condition as expected revealed a main effect of condition ($F(1,30)=9.85$, $p=0.004$) with the substitution condition exhibiting more pronounced activity than the control condition. Similar to the functionally defined IFG ROIs an interaction of condition and group ($F(1,30)=5.56$, $p=0.025$), showing a more pronounced condition difference in good than poor readers was found. The overall activation did not differ between ROIs but tended to be stronger in poor readers ($F(1,30)=3.27$, $p=0.080$).

2.4.4 Lateralization index in the frontal cortex

The activities in the left and right frontal lobes were compared by computing the lateralization indices for both condition contrasts vs. baseline. Three PR and five NR (and one child from the gap group) were excluded from lateralization analyses as

they did not show activation for both conditions at $p<0.001$. The average lateralization index for NR (LI substitution: 0.77±0.23; control: 0.62±0.58) pointed to a clear left hemispheric dominance. PR showed a more bilateral activation pattern (LI substitution: 0.03±0.49; control 0.31±0.45) especially for the more demanding substitution condition. The independent t-test revealed a highly significant group difference for the substitution condition only ($p<0.001$). Reading scores significantly correlated with the lateralization index of the substitution condition ($p=0.001$*, r=0.614) (Fig. 3D).

The 2x2x2 MANOVA (condition x hemisphere x group) showed that the number of activated voxels was greater for PR than NR ($F(1,22=8.5$, $p=0.008$), for substitution than control trials ($F(1,22)=4.54$, $p=0.044$) and within the left than right frontal cortex ($F(1,22)=12.6$, $p=0.002$). In addition, an interaction of condition and hemisphere ($F(1,22)=6.5$, $p=0.018$) was found, indicating more activated voxels in the left hemisphere for the substitution condition. Posthoc t-tests confirmed the significant hemispheric difference for the substitution condition ($p=0.001$) and showed that poor readers activated more voxels for the control condition in the left hemisphere ($p<0.001$) and for both conditions in the right hemisphere (substitution: $p=0.029$; control: $p=0.006$).

2.5. Discussion

Phonological processing is a well-known prerequisite for successful reading acquisition in alphabetic languages and phonological deficits are considered as the core deficit in dyslexia (Wagner and Torgesen 1987). In this study we examined brain correlates of phonological processing using a covert reading and mental letter substitution task in groups of young age-appropriate and poor reading children with little reading experience in their second year of formal reading training at school. In line with our expectations, reading skills of the 2nd graders were highly correlated with measures of phonological awareness confirming the importance of phonological skills during reading of beginners. Poor readers not only exhibited lower reading and phonological scores but also poorer writing skills, lower verbal IQs and slower rapid naming speed as compared to normally reading peers. The children performed well during the imaging sessions, given the demanding task involving reading and memorizing words or pseudowords, mentally substituting a letter and performing a

lexical decision. The strong correlation of in-scanner task performance and phonological score provides evidence that phonological processing critically contributes to a successful task performance.

Table 3:
MNI coordinates and anatomical brain regions for fMRI activation maxima of the condition difference ($p<0.0005$, $k\geq15$), the group comparison ($p<0.005$, $k\geq24$) and the regression ($p<0.005$, $k\geq24$) shown in Fig. 2 A-G (A-C; $p<0.0005$, $k\geq15$; D-G; $p<0.005$, $k\geq24$).

Region	Hemisphere	MNI			T	k (cluster size)
		x	y	z		
(A) All children substitution						
Substitution						
Superior frontal gyrus	L	-3	15	54	8.56	8
Middle frontal gyrus / Inferior frontal gyrus	L	-42	0	42	8.13	1218
Precuneus	L	-30	-48	45	4.96	83
Superior parietal lobule / Inferior parietal lobule	R	33	-54	48	4.80	46
Inferior frontal gyrus	R	42	6	33	4.46	15
Further activations were found in the caudate, cerebellum, red nucleus.						
Control						
Superior parietal lobule / Inferior parietal lobule	L	-30	-51	42	5.43	105
Middle frontal gyrus / Precentral gyrus	L	-48	3	51	5.36	178
Superior parietal lobule	R	33	-57	48	5.21	58
Middle frontal gyrus / Superior frontal gyrus	R	-6	12	54	4.96	95
Middle frontal gyrus	R	54	24	36	4.31	21
Substitution - Control						
Superior frontal gyrus /Middle frontal gyrus	L	-3	3	66	5.83	279
Insula (INS) /Inferior frontal gyrus (aIFG; pIFG)	L	-33	21	12	5.77	2106
Further activations were found in the caudate, thalamus, putamen.						
(B) Normal readers						
Substitution						
Inferior frontal gyrus /Middle frontal gyrus	L	-60	6	24	7.37	229
Superior frontal gyrus	L	-6	9	66	5.98	88
Substitution – Control						
Inferior frontal gyrus	L	-54	30	15	7.72	348
Precentral gyrus	L	-51	-3	48	5.68	28
(C) Poor readers						
Substitution						
Inferior frontal gyrus /Middle frontal gyrus	L	-51	9	36	6.73	81

Superior frontal gyrus	R	6	15	54	6.38	165
Insula	L	-42	15	3	4.81	32
Further activations were found in the caudate.						
Control						
Inferior parietal lobule	L	-33	-48	39	7.05	53
Precentral gyrus / Middle frontal gyrus	L	-51	12	39	5.28	106
Middle temporal gyrus	L	-66	-36	-6	5.17	29
(D) Group comparison NR>PR Substitution - Control						
Inferior frontal gyrus	L	-60	6	27	3.41	41
Middle frontal gyrus	L	-42	0	42	3.32	29
(E) Group comparison PR>NR Substitution						
Superior temporal gyrus	L	-60	-15	-3	4.55	120
Cuneus	L	-24	-93	30	4.47	32
Superior temporal gyrus	R	63	-21	0	4.27	246
Middle frontal gyrus	R	42	18	27	3.97	304
Middle frontal gyrus	R	24	57	27	3.83	35
Superior frontal gyrus /Middle frontal gyrus	R	24	27	57	3.78	94
Precentral gyrus	R	39	-18	39	3.67	120
Precuneus / Postcentral gyrus	R	3	-36	48	3.60	187
Precentral gyrus	R	39	-9	63	3.59	52
Superior parietal lobule	L	-39	-60	57	3.51	27
Precuneus	R	6	-63	42	3.10	73
Superior occipital gyrus /Precuneus	R	36	-78	30	3.28	57
Superior temporal gyrus /Middle temporal gyrus	R	60	-36	12	3.25	55
Precentral gyrus / Postcentral gyrus	L	-39	-18	42	3.21	44
Control						
Superior temporal gyrus	L	-60	-18	0	5.52	960
Superior temporal gyrus /Middle temporal gyrus /Precentral gyrus	R	60	-18	3	4.14	483
Middle frontal gyrus / Precentral gyrus	L	-54	18	30	3.98	98
Middle frontal gyrus / Insula /Middle frontal gyrus	R	42	18	24	3.58	149
Superior temporal gyrus	R	60	-42	15	3.49	49
Further activations were found in the caudate.						

(F) Positive correlation with reading score Substitution – Control						
Inferior frontal gyrus	L	-48	27	18	3.62	31
Inferior frontal gyrus /Insula	L	-60	6	27	3.52	52
(G) Negative correlation with reading score Substitution						
Superior frontal gyrus /Middle frontal gyrus	R	24	24	57	4.76	259
Precuneus /Paracentral lobule / Precuneus	R	3	-36	48	4.15	341
Postcentral gyrus	R	39	-36	69	3.98	42
Precentral gyrus	R	39	-15	39	3.73	63
Superior temporal gyrus /Middle temporal gyrus	R	63	-21	-3	3.65	170
Precuneus	R	3	-63	39	3.57	169
Precentral gyrus		39	-12	63	3.55	32
Precuneus /Angular gyrus /Superior parietal lobule	R	42	-75	39	3.49	95
Superior parietal lobule	L	-36	-57	54	3.46	25
Middle frontal gyrus	R	45	15	30	3.38	95
Precentral gyrus	R	57	-9	30	3.15	35
Precentral gyrus	L	-39	-18	42	3.09	24
Control						
Precentral	R	42	-15	39	4.99	783
Superior temporal gyrus	L	-66	-42	12	4.56	364
Postcentral gyrus / Precentral gyrus / Middle frontal gyrus	L	-57	-12	27	4.35	375
Precentral gyrus	R	27	-21	75	4.26	24
Superior parietal lobule /Inferior parietal lobule	L	-39	-60	57	4.26	73
Paracentral gyrus		0	-42	54	4.09	50
Insula	R	39	-30	18	3.94	35
Postcentral gyrus	R	45	-30	63	3.91	46
Precentral gyrus	L	-24	-24	75	3.86	24
Transverse temporal gyrus	L	-36	-36	12	3.34	35
Superior temporal gyrus	R	48	12	0	3.19	25
Middle frontal gyrus	L	-24	18	39	3.19	2
Superior frontal gyrus	R	6	51	54	3.15	37
Further activations were found in the caudate.						
Note: L=left hemisphere, k=cluster size						

2.5.1 Inferior frontal activation and phonological processing

The condition difference indicated more pronounced activity for substitution trials in a left frontal language network including the superior, middle, and inferior frontal gyrus as well as the insula. No occipito-temporal areas were specifically activated by the substitution trials confirming that children did not use purely visual strategies for task completion. Because only substitution trials required an additional demanding phonological manipulation of a memorized word or pseudoword before lexical access, we strongly suggest that the more pronounced left frontal activation revealed during substitution trials predominantly reflects phonological processing. These results are in line with several previous studies discussing the role of the inferior frontal gyrus in language processing (Bokde et al. 2001; Devlin et al. 2003; Poldrack et al. 1999) and the meta-analysis of Vigneau (Vigneau et al. 2006) relating phonological processing to activity along the precentral gyrus and the dorsal triangular part of the inferior frontal gyrus. Because of the changing lexical status and/or semantic content within substitution trials only, it is difficult to disentangle purely phonological and semantic activations. An influence on the brain response to substitution trials by semantic or lexical conflict during implicit mental matching of the word/pseudoword before and after letter substitution cannot be excluded. But semantic operations (Jobard et al. 2003; Poldrack et al. 1999; Vigneau et al. 2006) have often been associated with more ventral and anterior parts of the inferior frontal gyrus (Fiez 1997; Vigneau et al. 2006). Apart from phonological the condition differences in the inferior frontal gyrus. This was also confirmed by the absence of correlations between the behavioural working memory measure (digit span) and phonological activation in the inferior frontal gyrus (aIFG and pIFG) or the insula. Furthermore, the short interval (250ms) between the offset of the initial word and the presentation of the single letter aimed to minimize working memory load.

Activation differences in the dorsal aspect of the left inferior frontal gyrus between normal and poor readers were observed for the contrast of substitution vs. control trials. The more pronounced activation for normal as compared to poor readers in the left IFG and its correlation with reading skills is in accordance with other studies comparing normal and poor reading children: Especially with demanding phonological tasks which accentuate the core problems of dyslexic readers (Backes et al. 2002; Booth et al. 2006; Cao et al. 2006; van der Mark et al. 2009) reduced

inferior frontal activation was found in poor reading children, thus underlining deficient phonological processing. Not only phonological processing but also semantic matching processes of the initially presented (pseudo-)word and the newly generated (pseudo-)word may have contributed to stronger frontal activation in fluent readers in the condition contrast (Shaywitz et al. 2002). When scrutinizing the brain areas that best differentiate between substitution and control conditions in the left IFG and insula it becomes clear that the group differences in the left IFG emerged mainly due to the absence of condition differences in poor readers. This pattern indicates similar processing of the substitution and control trials in poor readers. More efficient processing of control trials in fluent readers was found not only in the functionally defined but also in the two literature-based ROIs (Richlan et al. 2009).

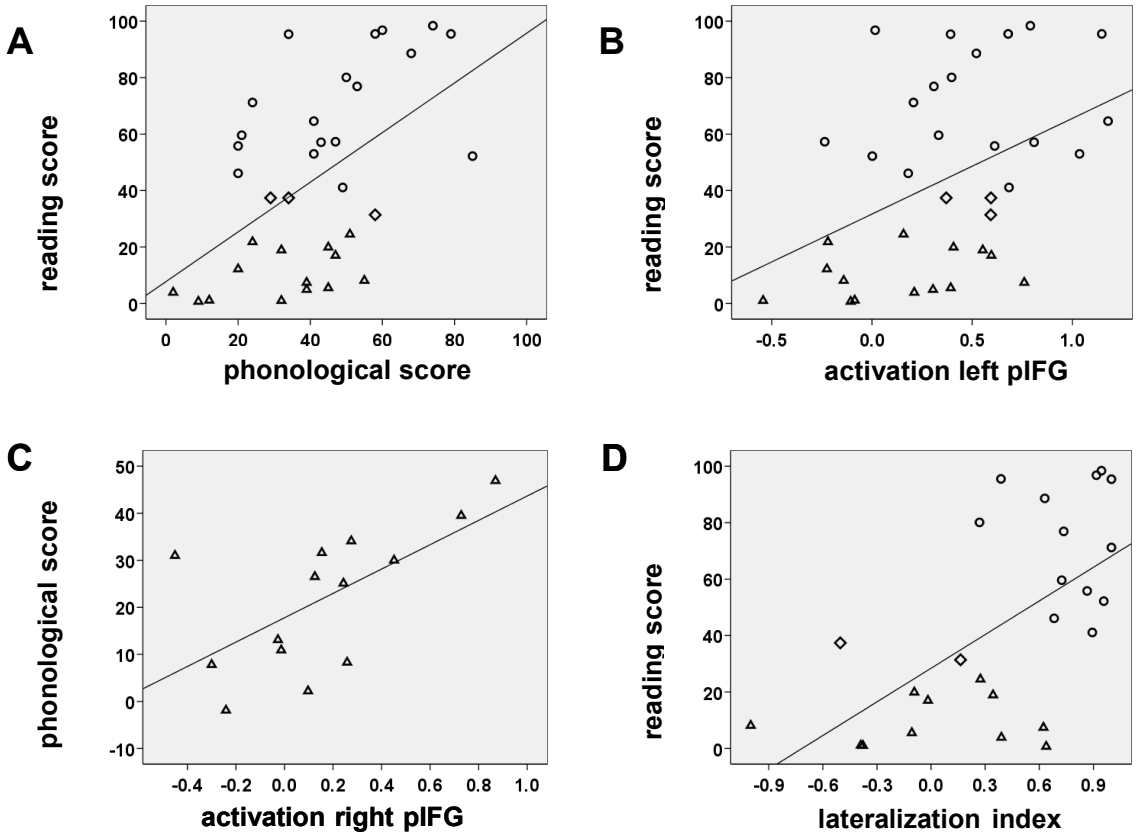

Figure 3:
(A) Correlation of the behavioural reading and phonological scores. (B) Correlation of the reading score with the activity (percent signal change) of the condition difference in the pIFG ROI. (C) Partial correlation (reading score as a covariate) of the activity (percent signal change) of the condition difference in the right pIFG ROI with the phonological score in poor readers (PR). (D) Correlation of the reading score with the lateralization index of the substitution condition. NR=circles, PR=triangles, gap group=diamonds.

2.5.3 Overactivation of poor readers in a bilateral frontotemporal network

The location of activation differences between groups for the phonological condition contrast are not in consonant with the recent meta-analysis (Richlan et al. 2009) that summarized the results of 17 original studies. Besides activation differences in temporal and parietal regions within the left and right hemispheres, Richlan et al. found the most consistent inferior frontal underactivation in dyslexic readers in the ventral opercular part of the IFG, while the adjacent dorsal opercular part and the more ventral anterior insula exhibited overactivation with dyslexia (Richlan et al. 2009). However, it is important to note that the meta-analysis by Richlan (2009) comprised a wide variety of studies that (i) examined children of different age groups, (ii) concentrated on different aspects of language processing, such as e.g. phonological or semantic processes, and (iii) contrasted experimental conditions to baseline or low-level control conditions (e.g. fixation or rest). Accordingly, differential activation reported for dyslexic vs. control readers reflects rather general differences in language processing while our task aimed to isolate specific phonological processes by using a high-level control condition. Consequently, when comparing the activation found for each condition vs. baseline, our poor readers exhibited more activation in an extended and bilateral frontotemporal network (Fig. 2E and 2G). The location of the overactivations largely correspond to the foci described by Richlan (Richlan et al. 2009), especially those in the left and right frontal cortices and the right middle temporal gyrus. In addition, also the left and right superior temporal cortices also exhibited overactivation in our poor readers. This dissociation between the activation in normal and poor readers indicates that poor readers had to invest more resources to accomplish the task independent of condition, resulting also in the lack of condition differences. With the present task design, we can not rule out that poor readers have chosen a different strategy to solve the task resulting in a different activation pattern. Such strategies may include to memorize only the part of the (pseudo-) word that remains the same and adding the subsequently presented letter prior to lexical decision in either condition or to articulate the items that had to be stored for subsequent phonological manipulations. The absence of differences in behavioural task performance between groups shows that, when different strategies were used by poor or fluent readers, these strategies were equally successful in terms of accuracy. Our behavioural data, however, did not allow drawing any

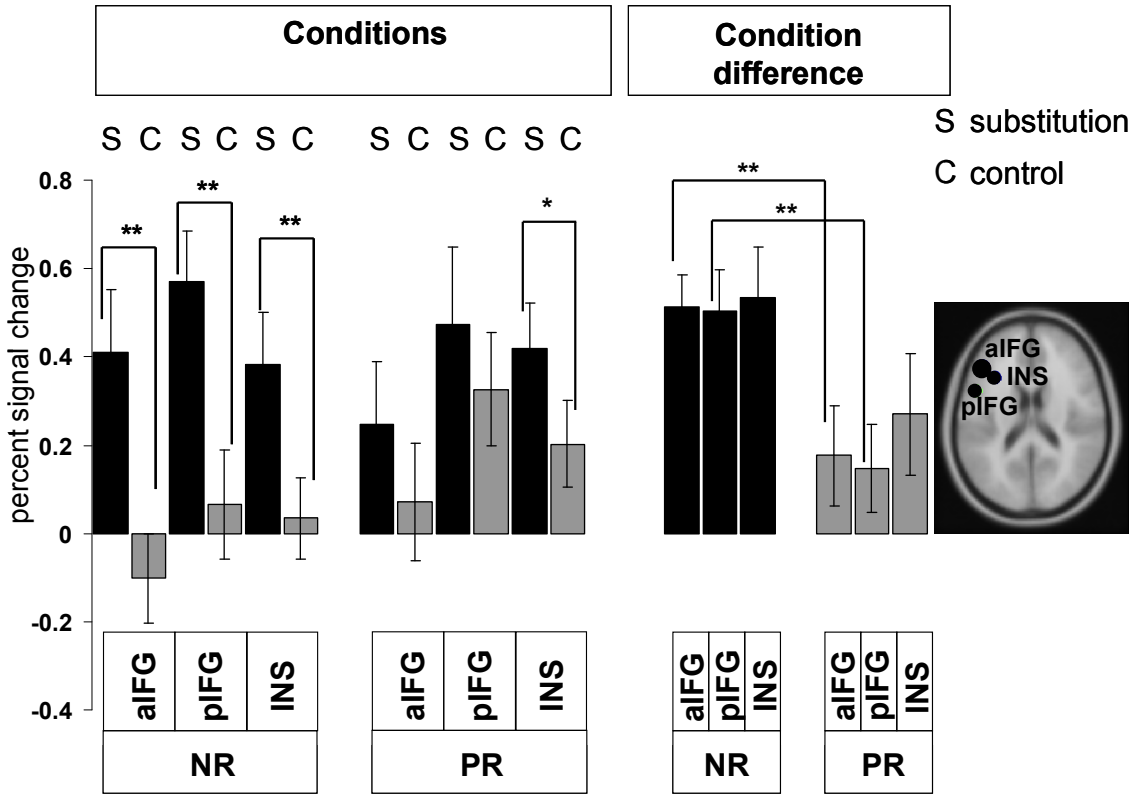

Figure 4:
The activation in the ROI of the left hemispheric aIFG, pIFG and INS for NR and PR are illustrated. The bars on the left represent the mean activity (percent signal change) for each condition separately (substitution: S, control: C), the bars on the right represent the condition difference (S vs. C) of the activity. Significant differences are marked with asterisks (posthoc t-tests: **p<0.01; *p<0.05). Error bars show the standard error of the mean.

conclusions about whether the speed of processing as a sign for efficiency differed between groups. It is very likely that our poor readers spent more resources in grapheme-phoneme decoding compared with their normal reading peers. This increased effort may at least partly explain the pronounced activation in the superior and middle temporal gyri of poor readers because these areas play an important role in grapheme-phoneme decoding (Jobard et al. 2003; Price, Wise and Frackowiak 1996; Rumsey et al. 1997; Sakurai et al. 2000). The strong bilateral activation of the superior and middle temporal gyri together with the activation in the motor cortex close to the mouth and larynx areas (Brown et al. 2008; Price 2010) in both conditions also indicates more overt articulation in poor readers in substitution and control trials to ease the subsequent manipulation and the retrieval of semantic information for lexical decisions (Ruff et al. 2008).

2.5.4 More bilateral activity in poor readers

The lateralization index confirmed the left hemispheric dominance of the substitution trials in beginning normal readers, which is in line with other studies examining normal reading children (Gaillard et al. 2003; Gaillard et al. 2001; Wood et al. 2004). This left lateralization also seen in the voxel wise analyses of the condition difference in the whole sample and in normal readers nicely corroborates previous studies reporting early emergence of the left hemispheric dominance in language networks (Brem et al. 2006; Brem et al. 2009; Holland et al. 2007; Ressel et al. 2008), even though the maturation of this lateralization continues until young adulthood (Brem et al. 2006). Poor readers exhibited a bilateral pattern with more activated voxels for both conditions indicating reduced left hemispheric specialization along with less focussed language processing, as can be seen in the overall activity of the groups for each condition separately (Fig. 2D and 2E). Accordingly, the lateralization index of the substitution condition also correlated with the reading score, pointing to increasing left hemispheric dominance for better readers.

mainly driven by the group of poor readers pointing to an increase in the right inferior frontal activity in relation to better phonological skills among poor readers. Although these correlations are weak and do not survive a stringent Bonferroni correction, the

Table 4:
Between-group differences (t-tests) of the percent signal change in the left hemispheric ROIs.

		NR Mean±SD	**PR** Mean±SD	***P***
aIFG	Substitution	0.41±0.60	0.23±0.14	0.428
	Control	0.10±0.43	0.07±0.13	0.299
	Substitution - Control	0.50±0.40	0.18±0.11	**0.014**
	P (Substitution vs. Control)	**<0.001**	0.143	
pIFG	Substitution	0.57±0.49	0.47±0.66	0.637
	Control	0.07±0.53	0.33±0.48	0.163
	Substitution - Control	0.50±0.40	0.15±0.38	**0.016**
	P (Substitution vs. Control)	**<0.001**	0.168	
INS	substitution	0.38±0.51	0.42±0.39	0.832
	Control	0.03±0.39	0.20±0.37	0.223
	Substitution - Control	0.54±0.48	0.27±0.14	0.143
	P (Substitution vs. Control)	**<0.001**	**0.025**	

direction of these results is important as they converge with a previous study suggesting that the involvement of right frontal areas in older poor reading children reflects an attempt to compensate for the deficient function of posterior brain areas during demanding phonological, semantic and lexical processing (Shaywitz et al. 2002). Moreover, our study extends previous findings in demonstrating that poor reading children already involve bilateral frontal areas 1.5 years after starting formal reading instruction, which clearly indicates that compensatory strategies develop in parallel with reading acquisition.

2.6. Conclusion

To conclude, this study demonstrates that the covert reading and mental letter substitution task is well suited to disclose phonological processing differences in the language network between young beginning, age-appropriate and poor readers. Clear differences pointing to deficits in phonological and lexical processing emerged in the left inferior frontal gyrus. In addition, poor readers not only exhibited a more bilateral activation pattern than normal reading children but moreover showed a pronounced overactivation in an extended bilateral frontotemporal network. This pronounced overactivation and the recruitment of right hemispheric brain regions suggest that poor readers spend more resources for successful grapho-phonological decoding and retrieval of lexical information. The tendency to involve right frontal brain areas when performing complex phonological processes indicates that compensatory strategies start to emerge at the very beginning of reading acquisition.

2.7. Acknowledgement

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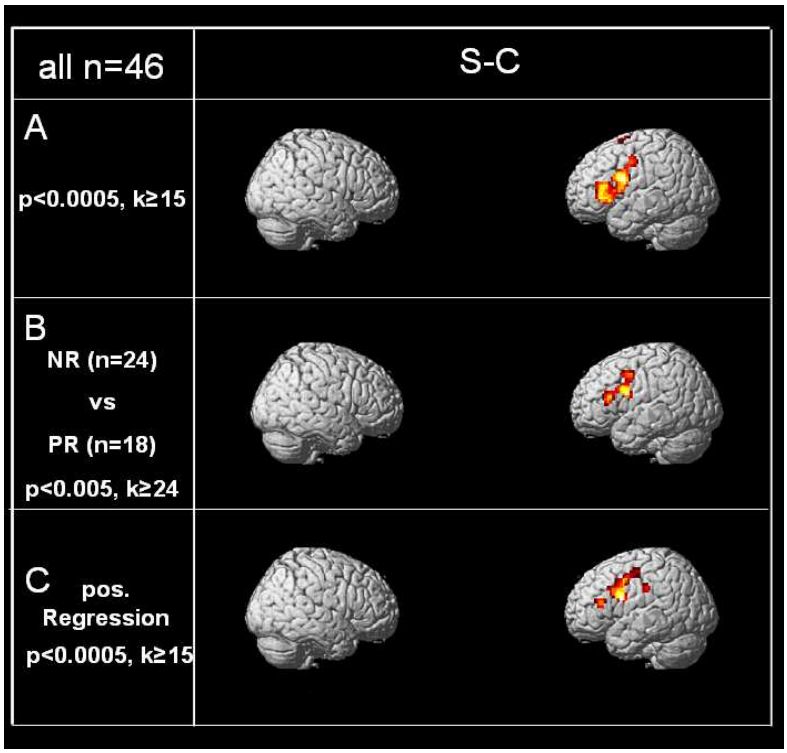
2.8. Supplementary material

A) *Analyses of the extended group (n=46)*

A supplemental analysis including the eleven children (all: n=46, NR n=24, PR n=18) that have been excluded because of poor (accuracy <65%) in-scanner task performance largely confirmed the results of the good performing (n=35) group. The eleven children that were excluded on the basis of poor performance in the fMRI task belonged to all three reading performance groups (NR n=6, PR n=4, gap group n=1) and did not show specific attentional problems according to the Child Behaviour Checklist CBCL (Achenbach 1991).

The whole brain analyses (Fig. A, Table A) revealed a similar pattern for the condition main effect in the insula, superior frontal gyrus, inferior frontal gyrus and additionally in the precentral gyrus and cingulate gyrus. Further also the group difference of the main condition contrast yielded a similar pattern with more



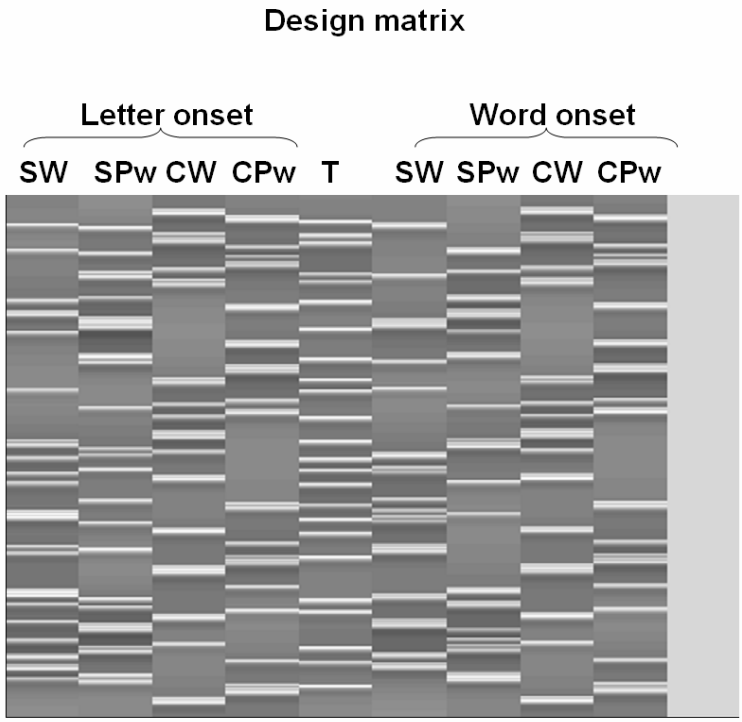
Supplementary Figure A:
A) The condition difference (substitution vs. control: p<0.0005, k≥15) for the extended sample, including those children with poor in-scanner task performance (n=46) revealed more activation for the substitution than the control condition in the insula, the superior frontal gyrus, inferior frontal gyrus as well as in the precentral gyrus and the cingulate gyrus B) The condition difference (substitution vs. control: p<0.005, k≥24) for the normal readers (n=24) revealed more activation in the inferior frontal gyrus compared to poor readers (n=18) C) The positive correlation of the condition difference with the reading score for the whole sample revealed that the inferior frontal gyrus and the precentral gyrus exhibited an activation increase with better reading skills (p<0.0005, k≥15).

pronounced activation in the left inferior frontal cortex. The regression analysis with the whole sample underlined the increasing activation in the left inferior frontal gyrus for substitution vs. control trials with reading skills.

When repeating the ROI analyses for the extended group with the same spherical ROIs as in the main text (aIFG, pIFG, INS), the 2x2 MANOVAs (group x condition) showed the expected condition main effect in all three ROIs (aIFG: $F(1,40)=19.4$, $p<0.001$, pIFG: $F(1,40)=25.0$, $p<0.001$ INS: $F(1,40)=26.8$, $p<0.001$) and the interactions of condition and group in both IFG ROIs (aIFG: $F(1,40)=8.2$, $p=0.007$; pIFG $F(1,40)=9.1$, $p<0.004$). Post-hoc t-tests showed significant condition differences in all three ROIs for NR ($p<0.001$), poor readers showed a significant condition difference in the INS only ($p<0.034$).

Appendix A:
MNI coordinates and anatomical brain regions for fMRI activation maxima of the condition difference, the group comparison and the regression for the group including the excluded children (n=46).

Region	**hemisphere**	**MNI**			**T**	**k (clustersize)**
		x	**y**	**z**		
all children (n=46; p<0.0005, k≥15): substitution > control						
insula / inferior frontal gyrus / precentral gyrus	L	-33	21	9	6.61	883
superior frontal gyrus / cingulate gyrus	L	-3	6	66	6.02	170
insula	L	33	21	6	4.30	19
Further activations were found in the putamen and thalamus.						
group comparison (p<0.005, k≥24): NR > PR						
inferior frontal gyrus	L	-45	27	15	4.27	282
positive correlation with reading score (p<0.0005, k≥15)						
inferior frontal gyrus / precentral gyrus	L	-57	6	24	5.04	251
middle frontal gyrus	L	-48	30	15	4.69	44
postcentral gyrus	L	-60	-24	36	4.19	20
Further activations were found in the caudate, thalamus and globus pallidus						
Note: L=left hemisphere, BA=Brodmann Area, k=cluster size						



Supplementary Figure B:
For the design matrix the onsets of the initial word/pseudoword and the onsets of the subsequently presented single letters of each of the four different trial types (SW: substitution resulting in W, SPw: substitution resulting in PW, CW: control W and CPw: control PW) as well as the target question marks were included as separate events, resulting in nine regressors.

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3 PRINT-SPECIFIC MULTIMODAL BRAIN ACTIVATION IN KINDERGARTEN IMPROVES PREDICTION OF READING SKILLS IN SECOND GRADE [*]

3.1 Abstract

Children who are poor readers usually experience troublesome school careers and consequently often suffer from secondary emotional and behavioural problems. Early identification and prediction of later reading problems thus is critical in order to start targeted interventions for those children with an elevated risk for emerging reading problems. In this study, behavioural precursors of reading were assessed in nineteen (aged 6.4±0.3 years) non-reading kindergarteners before training letter-speech sound associations with a computerized game (Graphogame) for eight weeks. The training aimed to introduce the basic principles of letter-speech sound correspondences and to initialize the sensitization of specific brain areas to print. Event-related potentials (ERP) and functional magnetic resonance imaging (fMRI) data were recorded during an explicit word/symbol processing task after the training. Reading skills were assessed two years later in second grade. The focus of this study was on clarifying whether electrophysiological and fMRI data of kindergarten children significantly improve prediction of future reading skills in 2nd grade over behavioural data alone. Based on evidence from previous studies demonstrating the importance of initial print sensitivity in the left occipito-temporal visual word form system (VWFS) for learning to read, the first pronounced difference in processing words compared to symbols in the ERP, an occipito-temporal negativity (N1: 188-281ms) along with the corresponding functional activation in the left occipito-temporal VWFS was defined as potential predictors. ERP and fMRI data in kindergarteners significantly improved the prediction of reading skills in 2nd grade over behavioural data alone. Together with the behavioural measures they explained up to 88% of the variance. An additional discriminant analysis revealed a remarkably high accuracy in classifying normal (n=11) and poor readers (n=6). Due to the key limitation of the study, i.e. the small group sizes, the results of our prediction analyses should be

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interpreted with caution and regarded as preliminary despite crossvalidation. Nevertheless our results indicate the potential of combining neuroimaging and behavioural measures to improve prediction at an early stage, when literacy skills are acquired and interventions are most beneficial.

3.2 Introduction

Poor reading not only contributes to troublesome school careers but is often accompanied by secondary emotional and behavioural problems (Arnold et al., 2005). A major goal is thus to predict poor reading as early as possible and to start targeted intervention programmes to prevent severe reading and associated problems. Among children, poor readers include the 4-10% suffering from developmental dyslexia, a severe developmental reading disorder (Klicpera et al., 2007; Schulte-Körne et al., 1998).

Several studies have reported on the prediction of later reading skills by means of behavioural data collected before school. Apart from the familial risk, e.g. socio-economic status (Catts et al., 2001) and behavioural measures collected at preschool age, such as letter identification, phonological awareness (Schneider, 1993; Wagner and Torgesen, 1987; Wagner et al., 1997) and rapid naming tasks (Manis et al., 2000; Puolakanaho et al., 2007; Savage and Frederickson, 2005; Wolff et al., 1990) have been shown to provide good estimates for reading outcome, with accurate classification rates of e.g. 75% (Pennington and Lefly, 2001) or even 93% (Catts et al., 2001). When socioeconomic status and vocabulary development were controlled for, phonological awareness assessed during kindergarten significantly predicted word identification and spelling skills eleven years later (MacDonald and Cornwall, 1995). Rapid naming has been reported to be an important predictor of both reading accuracy and reading speed (Furnes and Samuelsson, 2009; Georgiou et al., 2008). In a recent study, rapid naming has been found to be a more robust long-term predictor compared to phonological awareness (Furnes and Samuelsson, 2010), a measure which has been reported to lose its predictive influence on reading difficulties after the early grades and, rather, predicts individual variation in early phases (Leppänen et al., 2006; Wimmer et al., 1991). Low letter knowledge before school has often been observed in children with severe problems in learning

grapheme-phoneme associations and has thus also been proposed as a valuable predictor of an increased risk of developing a reading disorder (Lyytinen et al., 2004).

Despite rapidly growing knowledge about structural (Raschle et al., 2011) and functional differences in brain networks (Guttorm et al., 2010; Guttorm et al., 2005; Guttorm et al., 2003; Maurer et al., 2003) even before learning to read, few studies have combined direct (electroencephalography: EEG) or indirect (functional magnetic resonance imaging: fMRI) measures of neuronal activation, and/or characteristics of brain structure with behavioural measures to improve the prediction of reading outcome. Electrophysiological measures with predictive value so far have mainly related to the processing of speech sounds. The lateralization of a late (540-630ms) positive auditory ERP discriminated newborns with and without familial dyslexia risk status (Guttorm et al., 2010; Guttorm et al., 2005; Guttorm et al., 2001; Guttorm et al., 2003). Furthermore, auditory evoked potentials of newborns discriminated the reading outcome at age 8 with 81% accuracy (Molfese, 2000). Finally the lateralization of the mismatch negativity (MMN) to speech stimuli in kindergarteners improved prediction of long-term reading outcome over behavioural data alone (Maurer et al., 2009) and correctly classified 81% of children at risk for dyslexia.

Beyond this, differences in brain structure or function measured with MRI may also improve the prognosis of long-term reading outcome: a priori defined morphometric measures of temporal and frontal areas in children between 6 and 16 years were able to classify dyslexics with 60% accuracy. By including behavioural measures such as age and IQ, the classification rate increased to 87% (Semrud-Clikeman et al., 1996). Hoeft and colleagues also showed that the combination of behavioural scores, grey and white matter morphological measures and functional activation explained 81% of the variance in the decoding ability, significantly more than behavioural data alone in children between 8 and 12 years (Hoeft et al., 2007). The latest work of the same group furthermore demonstrated that brain measures such as the activity in the right prefrontal cortex together with the white-matter organisation of the right superior longitudinal fasciculus rather than behavioural measures alone, significantly predicted reading gains of dyslexics (Hoeft et al., 2011) thereby clearly demonstrating the potential of brain measures for neuroprognosis.

Other recently published studies have also pointed to functional activation and structural measures that are promising for prediction. An fMRI study by Specht et al. (Specht et al., 2009) revealed a negative correlation of the strength of activation in

the occipito-temporal cortex and the dyslexia risk index and a structural MRI study reported significantly reduced grey matter volume in the left occipito-temporal and bilateral parieto-temporal cortex, the left fusiform gyrus and the right lingual gyrus in familial at-risk children in preschool (Raschle et al., 2011). Interestingly, most areas with diminished grey matter volume in at-risk children, and especially the basal left occipito-temporal cortex often referred to as the visual word form system (VWFS) (Cohen et al., 2000; Vinckier et al., 2007), plays a key role in print processing when children learn to read (Brem et al., 2010; Maurer et al., 2006). Several neuroimaging studies have revealed hypoactivation in posterior left-hemispheric regions in dyslexics (Kronbichler et al., 2006; McCrory et al., 2005; Shaywitz et al., 2002), and diminished functional activation of the VWFS in response to print has often been associated with poor reading skills across different languages (Paulesu et al., 2001; Shaywitz and Shaywitz, 2005) and different writing systems (Hu et al., 2010). The corresponding N1 (~170ms) ERP attenuation and its magneto-encephalographic homologue also point to diminished sensitivity to print in dyslexics (Helenius et al., 1999; Kronbichler et al., 2006; Maurer et al., 2007; van der Mark et al., 2009). Furthermore, the following evidence points to the potential of occipito-temporal activity for predicting reading skills at a young age: i) structural alterations within the VWFS of at-risk children before school enrolment (Raschle et al., 2011); ii) its importance in learning to read supported by the early and rapidly emerging sensitivity to letters or letter strings (Brem et al., 2010; Cantlon et al., 2011); iii) the neurophysiological differences between normal readers and dyslexics seen in the corresponding N1 ERP (Maurer et al., 2007). Because interventions for poor readers might be most beneficial when started in parallel with reading acquisition (Bradley and Bryant, 1983) the identification of predictors at preschool age would be particularly valuable. In this study, kindergarteners trained with a computerized grapheme-phoneme association game called Graphogame (Lyytinen et al., 2009; Lyytinen et al., 2007; Saine et al., 2011) which initiates and sensitises specific brain areas to print processing (Brem et al., 2010). After eight weeks of grapheme-phoneme training, the emerging neural correlates of print processing were examined with ERP and fMRI in the non-reading children by using an explicit word processing task with strings of symbols serving as the control condition. We then for the first time combined behavioural, electrophysiological and functional MRI measures at

preschool age to examine whether the prediction of future reading skills could be improved.

3.3 Materials and methods

3.3.1 Study design and subjects

Forty native (Swiss-)German speaking kindergartners (mean age 6.4±0.3 years, 20 girls, 4 left-handed) took part in a larger longitudinal cross-over training study (also described elsewhere Brem et al., 2010) with two different non-commercial child-friendly, computerized training games (the “Graphogame” teaching grapheme-phoneme correspondences (Lyytinen et al., 2009; Lyytinen et al., 2007; Saine et al., 2011) and the control game teaching numbers and calculations (Räsänen et al., 2009)), behavioural and/or imaging sessions at kindergarten age and a behavioural follow-up in 2nd grade. Nineteen of these children (mean age 6.4±0.3 years, 14 girls, all right-handed) were selected for the current analyses because they had completed both an EEG and an fMRI session including an explicit word/symbol processing task after 8 weeks of grapheme-phoneme training (Lyytinen et al., 2009; Lyytinen et al., 2007; Saine et al., 2011) with appropriate data quality and task performance. Depending on children’s assignment in the longitudinal cross-over training study, after the initial behavioural assessment the children had started either with a period of grapheme-phoneme or a control training for proper balancing of the cross-over training study (for details about the training procedure see (Brem et al., 2010)).This design allowed us to assess all children after a highly consistent and well-defined literacy training phase focusing on grapheme-phoneme correspondence rather than reading. Children playing with the Graphogame first (8 children) performed the EEG/fMRI i.e. approximately 108.0±78.3 days after the behavioural assessment (mean age 6.6±0.3 years). When playing the control number game first (11 children) the relevant EEG/fMRI session took place after the second training interval, i.e. 125.0±16.1 days after the behavioural assessment (mean age 6.7±0.3 years). The separate EEG and fMRI recordings after the Graphogame training took place within 4.0±3.0 days (order of EEG, fMRI recordings counterbalanced: eight of the 19 children started with the EEG). At the time of the longitudinal behavioural follow up in 2nd grade the children were 8.4±0.3 years old. Note, all children also performed an

audiovisual implicit word and falsefont processing task in the imaging sessions before and after the training periods as described elsewhere (Brem et al., 2010).

At kindergarten a behavioural test battery was conducted with all children prior to the start of the trainings. In addition, the parents rated their children's behaviour by the Child Behaviour Checklist (CBCL) (Achenbach, 1991) and retrospectively estimated their own reading and writing competencies in school (adult reading history questionnaire, ARHQ) (Lefly and Pennington, 2000). Screening with the CBCL (Achenbach, 1991) attention score showed that all children had attention scores below the clinical cut-off (≤67). Based on the parents' ARHQ mean score (≥ 0.4) 3 of the 19 children were classified to have a "familial risk" for dyslexia (at-risk). And one of these "at-risk" children was classified as a poor reader two years later. The years of parental education served as an estimate of children's socioeconomic background (SES) (Brem et al., 2010). Further we rated the literacy environment based on the number of books of the parents and the children themselves.

The behavioural assessment was accomplished at children's home, where also the imaging procedures were explained to the children with pictures. Behavioural measures assessed in all kindergarteners before starting the trainings ("pre-training") were IQ (CPM: Coloured Progressive Matrices, children with an IQ ≥80 were included in the study) (Raven, 2002), receptive vocabulary and word comprehension (two subtests of the "Marburger Sprachverständnistest für Kinder, MSVT") (Elben and Lohaus, 2000), rapid naming of objects (RAN), letter knowledge (LK: including upper and lower case letters whereby letter sound and letter name were considered as correct responses), reading (tested with a word reading subtest of the "Salzburger Lesetest, SLT") (Landerl et al., 1997) and precursors of reading and writing skills as implemented in the BISC screening test battery ("Bielefelder Screening zur Früherkennung von Lese-Rechtschreibschwierigkeiten, BISC": a screening test battery for the early detection of children with an elevated risk to develop reading and writing difficulties at school age. This test battery allows to determine a risk score ("BISC risk") at kindergarten age. The BISC risk score is a composite score computed by the performance in several subtests such as pseudoword repetition, rhyming of word pairs, visual word comparison, phoneme association, colour naming, syllable segmentation, phoneme extraction (Jansen, 1999)). For further analysis we used the BISC risk point score (the "BISC risk score" can be computed by the performance of a child in all subtests and indicates whether a child has a high risk for

developing reading and/or spelling difficulties) and two summary measures reflecting either phonological awareness in a broad sense (PAbs) or phonological awareness in a narrow sense (PAns). PAbs is linked to speech skills associated with rhyming and clapping games and is thus formed by the sum raw scores of the subtests rhyming of word pairs and syllable segmentation. The PAns is considering the analysis of the phoneme structure without a rhythmic, segmental language context and is defined by the summed raw scores of the subtests phoneme association and phoneme extraction (Jansen, 1999). LK (upper and lower case) and reading skills were assessed before and after the Graphogame (in either the EEG or fMRI session). The gain in LK was determined as the difference between post- and pre-training LK. Before training and also after the grapheme-phoneme training period (n=19: average training time: 321.5±124.3 min; average training period: 54.4±8.5 days) children were “non-readers”, i.e. no child was able to read more than 6 out of 30 words (high-frequency nouns of a German word reading test, the SLT (Landerl et al., 1997)) when given as much time as needed two children showed very rudimental reading skills after training as they were able to decode 8 or 17 out of 30 words. Note, reading in Switzerland starts in first grade, i.e. at the age of 7 years.

Analogous to our previous study (Bach et al., 2010) children scoring above the 40th percentile in the standardised reading test in 2nd grade (number of correctly read words per minute, subtest of SLT (Landerl et al., 1997)) were considered as normal readers (NR=11), children scoring below the 25th percentile as poor readers (PR=6) (Bach et al., 2010; Manis et al., 1996; Shaywitz et al., 2003). The children scoring between the 25th and the 40th percentile were assigned to the gap group (GG=2) and excluded for all group comparison analyses.

3.3.2 Task

Besides an audiovisual modality judgment task described elsewhere (Brem et al., 2010) children performed an explicit word/symbol processing task. The explicit word/symbol processing task was only conducted in the imaging session after the grapheme-phoneme training period (Fig. 1). Children were instructed to try to decode the presented words (W) and to decide by the left/right button press of their left/right index finger whether it referred to an animal or not. In general, despite the relatively long presentation time children were not able to read the short, high-frequency nouns

but they tried to decode (guess). In the control condition the children solved a visual symbol (S) discrimination task and indicated by button press whether strings of hash signs (#) contained an asterisk (##*#) or not (####).

The assignment of response buttons was counterbalanced across the children but kept constant for the EEG and fMRI measurements (9 of 19 children pressed left for an animal word). Words and symbols in black were presented in the middle of a white screen for 5250ms while static pictures of a dog/crossed out dog and strings of hash signs with/without asterisk (to remind the children which button to press) were always visible on the screen, also during the ISI of 500ms in which a fixation cross was shown. The two conditions were presented pseudo-randomly. The EEG task consisted of two parts (task duration 2x6.33 min) in order to have enough stimuli (40 stimuli/condition) to compute ERPs. In addition, 26 null events were pseudorandomly interspersed. Children were allowed to take a short break in between the parts. The event-related design of the fMRI task included 20 stimuli/condition and 36 null events pseudorandomly interspersed (task duration 7.28 min). To verify that only children who attended and responded to the stimuli were included in the analyses, a minimum overall accuracy of 65% correct responses to symbols served as inclusion criteria (for subject inclusion criteria, omissions were counted as incorrect responses). No specific performance criteria were set for words as children were not able to read. The analyses on accuracy in task performance concentrated on those trials for which a behavioural response was given only, but also the rate of omissions is reported. Multivariate analyses of variance (MANOVA) were calculated separately for task performance (accuracy, omissions) in the EEG and fMRI sessions (factors condition and group).

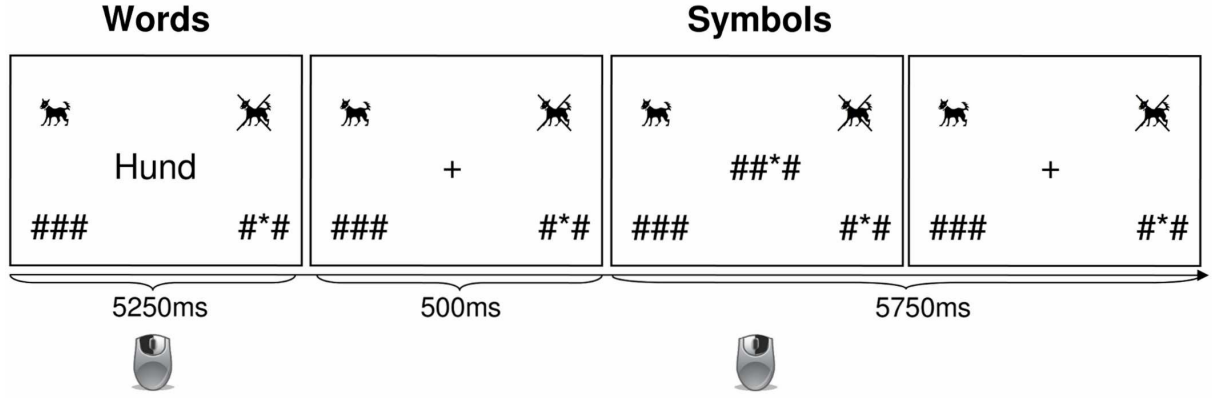

Figure 1:
Task procedure: short words (W) and symbol strings (S) were pseudorandomly presented to the children. The children decided whether the symbol strings contained an asterisk (*) (right button press) or not (left button press) and tried to decide whether the word denoted an animal (left button press) or not (right button press).

3.3.3 EEG Recording and processing

The children sat in front of a computer screen (distance 120cm). The ERPs were recorded from 64 channels at 500Hz (recording reference Fz recomputed offline to average reference, ground: AFz, filters 0.1-70Hz, impedances below 15kΩ). Post-processing included down-sampling to 256Hz, filtering 0.1-30Hz, artefact rejection (100μV; for two children 125 μV) and correction of eye movements using ICA (Jung et al., 2000). A minimum of 15 epochs per condition (mean W: 29.7±6.4; S: 30.1±6.5) was required for computing condition averages. The EEG was recorded using caps which included all 10-20 system electrodes as well as supplemental electrodes FPz, FCz, CPz, POz, Oz, Iz, AF1/2, F5/6, FC1/2, FC3/4, FC5/6, FT7/8, FT9/10, C1/2, C5/6, CP1/2, CP3/4, CP5/6, P5/6, TP7/8, TP9/10, PO1/2, PO9/10, OI1/2, PPO9h/10h and two EOG electrodes below the outher cantus of each eye. To provide a better coverage O1′/2′ and Fp1′/2′ were placed 15% more laterally to Oz/Fpz. At the midline in between Oz and Iz, OI1 and OI2 were placed to more evenly cover the occipital scalp.

The data was epoched (-100ms to 1500ms after the stimulus) and transformed to the average reference (Lehmann and Skrandies, 1980) before computing separate averages for words and symbols. The N1 interval was defined as the interval between two subsequent global field power (GFP) sinks (188-281ms) in the grand mean waveform for words and symbols. As in our previous studies (Brem et al., 2010; Maurer et al., 2006) the mean amplitude of the N1 interval within a left occipito-temporal electrode cluster (LOT: O1', P7, PPO9h, PO9) was determined for each condition and the condition difference (W-S). These mean values in the N1 at LOT were subjected to a condition by group MANOVA. To examine whether the N1 at LOT was correlated with phonological measures (risk point score, PAbs, PAns), language related skills (receptive vocabulary, word comprehension, RAN, LK and LK gain measures) or training time correlations were computed. Further the N1 was used as a predictor in regression and discriminant analyses.

3.3.4 FMRI Recording and processing

The fMRI data was acquired on a 3-T scanner (GE Medical Systems) using an echo planar imaging sequence (25 axial slices covering the whole brain, TR 1500 ms, TE

31, matrix 64x64, voxel size 3.75x3.75x5mm, slice thickness/gap 4.6/0.4 mm, flip angle 50°, FOV 240 mm2). The children were stabilised using custom-made padding and fixations. Earplugs, headphones and a noise insulation mat protected the child from scanner noise. Visual stimulation was presented with MR compatible (TFT) video goggles. During the task responses were collected by a response box. The children were accustomed to the scanner by a demonstration of the scanning procedure with a teddy bear.

SPM5 (Wellcome Department of Cognitive Neurology, London, http://www.fil.ucl.ac.uk/spm) was used for processing and analysis. The first 4 scans were always excluded to avoid T1 saturation effects, images were slice-time corrected, realigned and normalised (7th-degree spline interpolation) to match the Montreal Neurological Institute template (MNI), resampled (3mm3 voxels) and smoothed with a 9mm FWHM isotropic Gaussian kernel. Based on the SPM realignment procedure, we included only those children for whom more than 97.5% of the total 295 scans did not exceed the threshold of maximum 2.5mm/2.5° translation/rotation displacement during task completion in the x, y or z plane. The few scans exceeding the translation/rotation threshold were substituted by neighbouring scans. The event-related activation of both conditions was modelled using the standard SPM hemodynamic response function and filtered with a 128-s high-pass filter. The second-level random effect analyses were based on the individual contrast images. The threshold ($p<0.005$, $k\geq29$) reported in our study is corrected for multiple comparisons by using a cluster extent threshold criterion determined by the Monte Carlo simulations procedure (in MATLAB, 10000 simulations) to enforce an a priori corrected threshold of $p<0.05$ (Slotnick et al., 2003; Slotnick and Schacter, 2004). The Talairach Daemon (Lancaster et al., 2000) was used to identify brain structures after transformation of the MNI coordinates into Talairach coordinates (by the mni2tal formula (http://eeg.sourceforge.net/doc_m2html/bioelectromagnetism/mni2tal.html)).

Percent signal change from six spherical (radius=5mm) regions of interest (ROI) was extracted on unsmoothed images for W and S by using MARSBAR toolbox (version 0.41), provided by M. Brett (http://marsbar.sourceforge.net). The selection of the ROI in the VWFS was based on previous literature (MNI x, y, z:-42, -54, -17) (Brem et al., 2009; Cohen et al., 2000; van der Mark et al., 2009) whereas the centres of the other five ROIs corresponded to the regional maxima of the functional activation difference

(W-S). To avoid circularity effects (Kriegeskorte et al., 2009; Vul et al., 2009) (factors condition and group) was performed for the literacy based VWFS ROI only.

The condition difference in the VWFS was further correlated with phonological measures (BISC risk point score, PAbs, PAns), language related skills (receptive vocabulary, word comprehension, RAN and LK and LK gain measures) and training time.

3.3.6 Prediction analyses

Pearson correlations: To determine the variables to be included in the subsequent multiple regression analysis, one-sided Pearson correlations were computed between each behavioural and demographic measure and the performance in the reading test in 2nd grade. These correlations are reported in Table 1.

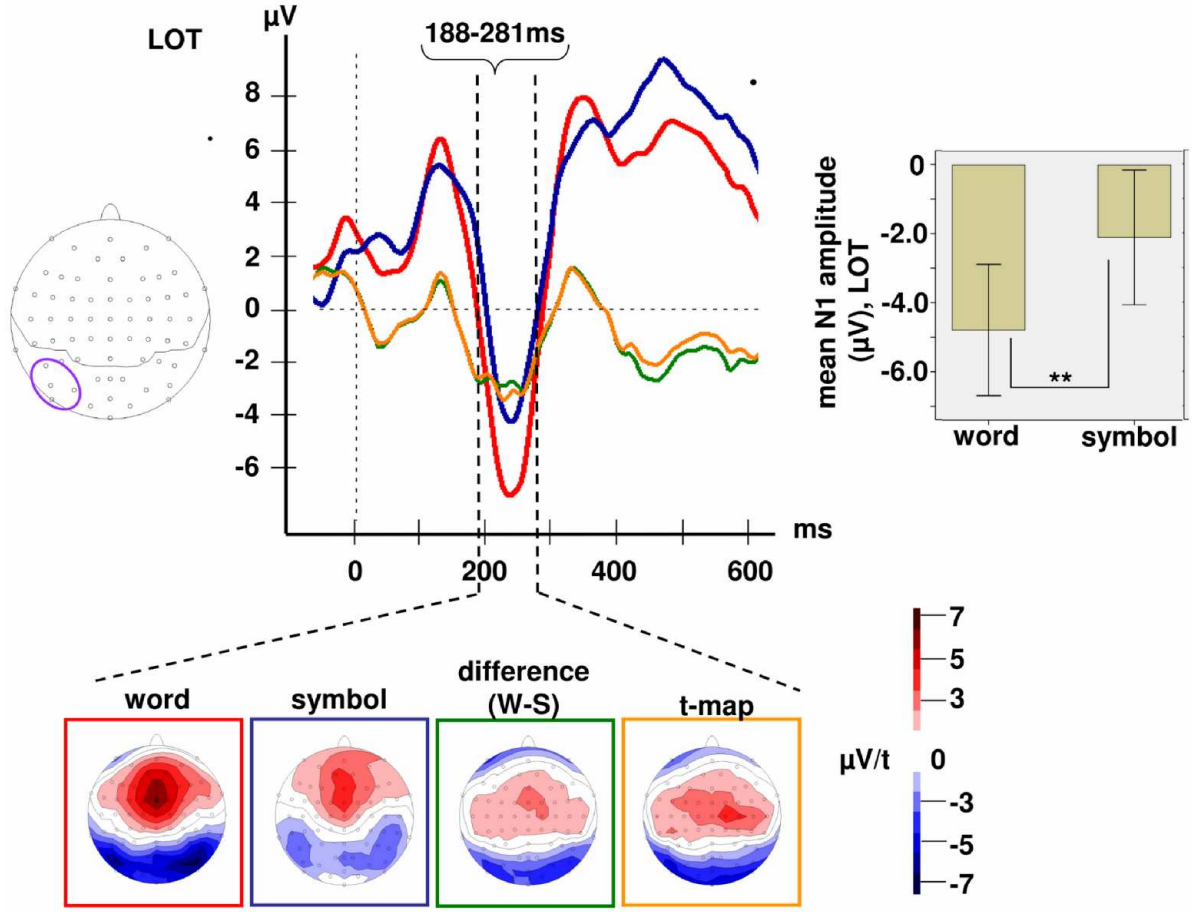

Figure 2:
(Upper) Event related-potentials at left occipito-temporal sites (LOT: mean of O1', P7, PPO9h, PO9) are illustrated: words (red), symbols (blue), the condition difference (green) and the t-values of the condition difference (orange). Bars on the right depict the mean amplitudes within the N1 interval to words and symbols. (** p<0.01). (Lower) Potential field maps (seen from top) of the mean amplitude values for W (red), symbols (blue), their difference (green) and t-maps (orange) of the N1 interval (188-281ms).

3.3.6 Multiple linear regression analysis

3.3.6.1 Forced entry method

The reading score (percentiles) of the 2nd graders was used as the criterion variable in our core multiple regression analysis. Only behavioural predictor variables showing significances in one-sided Pearson's correlations with the reading score in 2nd grade (Table 1) were used for this multiple regression analysis. To limit the number of variables again, we only used the summary measures for phonological processing (risk point score, PAbs and PAns) instead of all significant single subtests and the total pre- and post-training LK (upper+lower case) or the total gain in LK.
For the multiple linear regression and the preliminary discriminant analyses we report both uncorrected and Bonferroni corrected p-values (accounting for the amount of selected predictor variables). Corrected values are marked with an asterisk (*) throughout the text and tables. Assumptions for regression analyses such as multicollinearity, homoscedasticity, independence and normal distribution of errors, tested by correlational matrices, Levene test and Durbin-Watson test, were met.

3.3.6.2 Hierarchical stepwise method

In addition to behavioural measures the N1 mean amplitude of the condition difference (W-S) between 188 and 281ms at LOT and the corresponding differential activity (W-S) of the VWFS ROI were used as neuroimaging predictors. To test whether N1 and VWFS measures significantly explained additional variance in the reading score in 2nd grade over behavioural measures alone, we used a stepwise procedure. Behavioural measures were entered as one block and the N1 and the VWFS activations were entered as separate blocks (adding $p<0.05$, keeping $p<0.10$ significant predictors).

3.3.6 Preliminary discriminant analyses

A preliminary discriminant analysis was conducted in order to classify future normal and poor readers (NR>40th percentile: n=11; PR<25th percentile: n=6). Given the limitations regarding validity and reliability of the performed discriminant analyses

with the small sample sizes used here, the results of this analysis are referred to as preliminary and therefore need to be interpreted with caution. The predictor variables were entered using minimised Wilks' lambda at each step. Normal distribution (Kolmogorov-Smirnov test) and equality of covariance matrices between groups (Box's M test) was confirmed for all variables of interest. Only variables contributing to the discrimination (probability for predictors to enter set at $p<0.05$, to remove at $p>0.1$) were included in the stepwise analyses. The leave-one-out method was used for cross validation.

3.4 Results

3.4.1 Behavioural task performance

The MANOVAs for accuracy (computed only for trials with a behavioural response) with factors group (11 NR/5 PR, one PR excluded due to a very high rate of omissions in word trials) and condition (W/S) showed a significant main effect of condition (EEG: $F(1,14)=43.4$, $p<0.001$; fMRI: $F(1,14)=27.9$, $p<0.001$). This main effect demonstrated that performance in symbol discrimination was better than in word classification (EEG accuracy: W=76.5±14.6%; S=96.8±4.5%; EEG omissions: W=51.1±26.2%; S=8.3±6.3%; fMRI accuracy: W=61.2±18.0%; S=93.0±8.2%; fMRI omissions: W=40.0±30.4%; S=5.0±5.8%). There was also a main effect of group ($F(1,14)=13.0$, $p=0.003$) and an interaction of condition and group ($F(1,14)=6.5$, $p=0.023$) for the EEG performance. The performance in classifying words was thus better in future NR than PR while symbol discrimination accuracy was similarly high in both groups. The MANOVA for omissions with factors group and condition showed a condition main effect with more omissions to word stimuli (EEG: $F(1,15)=55.5$, $p<0.001$; fMRI: $F(1,15)=24.7$, $p=0.001$). The high rate of omissions indicated that children pressed too late or remained indecisive and did not respond whenever they felt insecure about the response. The excellent performance in symbol discrimination and the above chance level performance for word classification also showed, that the children were able to follow the task instructions.

3.4.2 EEG results

A more pronounced activity to words vs. symbols was found over the occipito-temporal cortex as visible in the t-maps and the t-curve at left occipito-temporal (LOT) sites in Figure 2. The MANOVA of the N1 mean value at LOT revealed a highly significant main effect of condition ($F(1,15)=9.9$, $p=0.007$) showing a more pronounced negativity to words than symbols. The condition difference at LOT correlated with RAN ($p=0.036$, $r=-0.423$), pre-training LK ($p=0.026$, $r=-0.454$; lower case $p=0.013$, $r=-0.510$) and post-training LK ($p=0.028$, $r=-0.446$; upper case $p=0.016$, $r=-0.494$).

3.4.3 FMRI results

The activation for words and symbols (Table 2, Fig. 3) comprised a bilateral network, mainly including occipital and frontal areas. The condition difference was dominated by activity in the left inferior frontal gyrus (IFG), the left and right medial frontal gyrus (MFG) as well as the left and right middle temporal gyrus (MTG) (Table 2). Print sensitive activity in the VWFS (fusiform gyrus) with more activity for W than S emerged at a slightly lower threshold ($p<0.005$, $k=26$) for the whole sample but reached a corrected significance level when looking at the kindergarten children with normal reading skills in 2nd grade (n=11) (Fig. 4). Note, no significant group difference in print specific activation was found in a whole brain analysis.

The MANOVA of the VWFS ROI showed a trend for a condition main effect ($F(1,15)=3.9$, $p=0.066$) with stronger activity for words. Further, VWFS activity correlated with the gain in letter knowledge of lower case letters after Graphogame training ($p=0.021$, $r=0.472$) and the BISC risk point score ($p=0.035$, $r=-0.424$).

3.4.4 Behavioural assessment data

Note, all correlation and prediction analyses that are based on behavioural assessment data in kindergarten and 2nd grade were also computed for a larger sample of 40 children and are reported in the supplementary information (SI) online (SI1).

The group comparisons as well as the correlation of each behavioural kindergarten

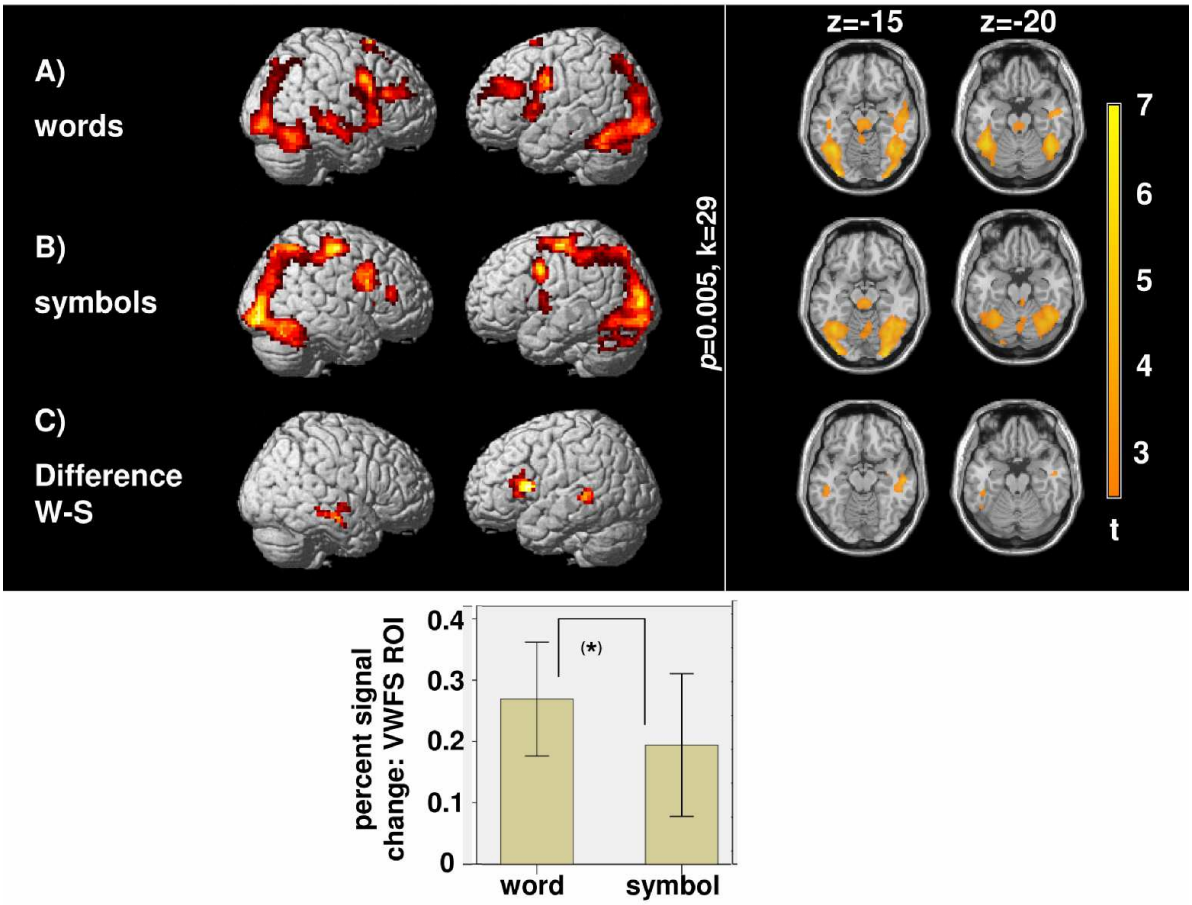

Figure 3:
(Upper) Brain activity elicited by (p<0.005, k≥29, t≥2.88) (A) word > rest, (B) symbol > rest and (C) the difference of words vs. symbols. The corresponding activations are listed in table 1. Horizontal sections on the right display the activation (thresholded from t=2.5 to t=7) in the VWFS. The bars below illustrate the percent signal change in the VWFS ROI for words and symbols ((*)=trend).

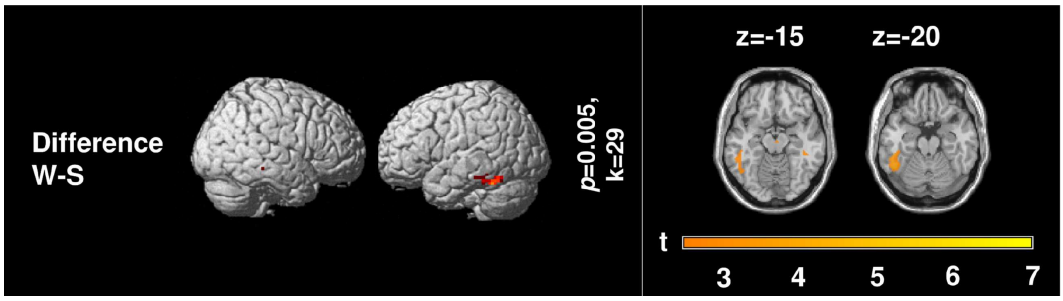

Figure 4:
Brain activity elicited by the difference of words vs. symbols in the group of future normal reading children (n=11, p<0.005, k≥29, t≥3.17). Horizontal sections on the right display the activation (thresholded from t=2.5 to t=7) in the VWFS.

measure with the 2nd grade reading score are summarised in Table 1. NR differed significantly from PR in RAN, receptive vocabulary, PAbs and pre-training lower case LK and tended to differ regarding the literacy environment of the child. The correlations with 2nd grade reading scores yielded significances for RAN, receptive

vocabulary, PAbs, PAns, pre-training lower case LK, pre-training total LK and all post-training LK measures.

A reliable increase in LK due to training was found for letter knowledge as shown by the paired t-tests of pre- vs. post-training letter knowledge measures (all $p<0.001$) and the significant correlation of training time with letter knowledge (post-training upper case LK $p=0.042$, $r=0.471$) and letter knowledge gain (total LK gain $p=0.025$, $r=0.513$).

Table 1:
Group comparison for demographics and behavioural tests for the imaging group.

	Groups according to reading scores in 2nd grade			**n=19**
Behavioural measures in kindergarten	**NR (n=11) (>40 Percentile)** Mean ± SD	**PR (n=6) (<25 Percentile)** Mean ± SD	***P (groups)***	***P one-sided Pearson's correlation with reading score in 2nd grade***
Reading score in 2nd grade (words per minute score **SLT**; percentile)	68.92±17.87	14.20±6.92	***<0.001***	
Pretest age (years at behavioural assessment at home)	6.35±0.29	6.33±0.19	*0.923*	*0.389*
Attention score (**CBCL**)	48.09±8.58	45.63±6.78	*0.555*	*0.314*
IQ (Raven) (ss)	56.77±9.19	56.00±6.14	*0.857*	*0.413*
ARHQ (mean)	0.26±0.10	0.29±0.11	*0.606*	*0.148*
Training time (minutes)	333.88±130.15	300.43±136.23	*0.625*	*0.254*
Rapid naming **RAN** (speed in seconds)	39.64±7.93	48.17±5.49	***0.034***	***0.008***
Receptive vocabulary (**MSVT**) (ss)	57.27±5.00	48.33±4.46	***0.002***	***<0.001****
Word comprehension (**MSVT**) (ss)	48.73±8.05	49.67±7.53	*0.817*	*0.639*
BISC risk score	1.45±1.69	2.17±1.17	*0.377*	*0.224*
Phonological awareness (broad sense) **PAbs**	17.82±1.94	14.17±2.93	***0.007***	***0.011***
Phonological awareness (narrow sense) **PAns**	19.18±1.08	17.50±2.26	*0.134*	***0.011***
Pre- training **LK** (lower case)	9.09±7.40	2.83±1.47	***0.020***	***0.008***

Pre- training **LK** (upper case)	11.73±8.92	10.67±6.71	*0.804*	*0.133*
Pre- training **LK** (total)	20.82±15.99	13.50±7.56	*0.311*	***0.038***
Post-training **LK** (lower case)	17.91±6.93	11.67±8.38	*0.119*	***0.031***
Post-training **LK** (upper case)	18.91±7.33	14.33±5.68	*0.206*	***0.012***
Post-training **LK** (total)	36.82±13.86	26.00±13.80	*0.144*	***0.018***
Socio-economic status (**SES**)	16.32±2.65	15.25±2.62	*0.438*	*0.131*
Number of books parents	4.18±1.17	3.33±1.51	*0.215*	*0.650*
Number of books child	4.55±0.93	3.50±1.22	*0.066*	*0.760*

Note: All behavioural measures have been collected before Graphogame training except for the post-training letter knowledge measures and training time.

CBCL Child Behaviour Checklist; **ARHQ** Adult Reading History Questionnaire; **MSVT** Marburger Sprachverständnistest für Kinder; **BISC** Bielefelder Screening zur Früherkennung von Lese-Recht-schreibschwierigkeiten; **Number of books** categorical measure (parents: 0=no books; 1=1-10 books; 2=11-50 books; 3=51-100 books; 4=100-200 books; 5= more than 200 books; child: 0=no books; 1=1-10 books; 2=11-20 books; 3=21-30 books; 4=31-50 books; 5= more than 50 books).
ss standard score (T = 50, SD = 10)
* Bonferroni corrected

3.4.5 Multiple linear regression analysis

Based on significant Pearson's correlations, the following behavioural measures were used as predictors (simultaneous forced entry of 5 predictors: RAN, receptive vocabulary, PAbs, PAns, LK, see Table 1). To minimise the total number of behavioural predictors we only entered one post-training LK (total) measure (but see SI2A for pre-training LK). Even though there was no significant correlation of letter knowledge gain (upper case, lower case or total letter knowledge gain) with reading score in 2nd grade we repeated this analysis and substituted post-training LK with the total gain in LK. The results of this subsidiary analysis corresponded to the core analysis (see SI2B).

3.4.6 Hierarchical stepwise method

The behavioural measures collected at kindergarten significantly predicted reading outcome in 2nd grade (R=.80, F(5,13)=4.7, p=0.011) and explained a considerable amount (adjusted R2: 51%) of the variance. Importantly, when adding N1 print sensitivity, the explained variance increased significantly to 67% (p=0.017). The

VWFS print sensitivity again significantly contributed to the prediction (p=0.003*) and increased the amount of explained variance to 84% (Table 3).

According to the standardised β-coefficients (Table 3) RAN (p<0.001*), the mean value of the N1 condition difference at LOT (p=0.001*) and the VWFS (p=0.003*) significantly contributed to the prediction in our model. Therefore they were chosen as predictor variables for a subsequent "preliminary" discriminant analysis to distinguish NR and PR.

Note, we repeated this analysis by substituting the VWFS ROI with each of the five functionally defined ROIs (see Table 2, W-S). Only the ROI in the left middle temporal gyrus significantly contributed to prediction: The left MTG print sensitivity together with the behavioural measures and the N1 explained 78% (p=0.027) of the variance (see also SI2C).

Table 2:
MNI coordinates and anatomical brain regions for fMRI activation maxima of words, symbols and the condition difference W-S (*p*<0.005, k≥29).

Region	**hemisphere**	**MNI**			**T**	**k**
		x	**y**	**z**		
Words (W)						
Cingulate gyrus	L	-6	18	48	9.38	1457
Insula	R	33	21	9	8.52	1219
Inferior occipital gyrus	L	-33	-93	-12	7.99	1335
Inferior occipital gyrus	R	36	-90	-12	7.64	1168
Insula	L	-30	18	12	6.80	947
Thalamus	R	6	-30	0	5.22	724
Symbols (S)						
Middle occipital gyrus	R	33	-93	-9	7.98	2597
Medial frontal gyrus	R	9	6	54	7.89	822
Precentral gyrus	L	-36	-12	63	6.97	2369
Inferior frontal gyrus	L	-48	3	36	6.38	162
Thalamus	R	9	-18	6	5.73	839
Inferior frontal gyrus	R	45	3	27	5.63	350
Insula	L	-42	-3	15	5.02	154
Cerebellum	R	3	-39	-27	4.82	45
Inferior frontal gyrus	R	48	36	12	4.53	59
Cingulate gyrus	R	6	-6	30	4.48	65
Cerebellum	R	0	-60	-36	4.01	41
Insula	R	36	18	9	3.82	36
Cerebellum	R	9	-57	-15	3.47	49
Condition difference (W-S)						
Medial frontal gyrus	R	15	33	33	5.05	134
Inferior frontal gyrus	L	-51	15	12	4.61	199
Middle temporal gyrus	R	51	-33	-9	4.55	130
Middle temporal gyrus	L	-54	-39	0	4.14	71
Medial frontal gyrus	L	-12	30	36	3.39	33
Note: L=left hemisphere, R=right hemisphere, MNI=Montreal Neurological Institute, k=cluster size						

3.4.7 Preliminary discriminant analysis

The following preliminary discriminant analysis did not include the two children with intermediate reading scores in between the 25th and the 40th percentile. The stepwise procedure showed, that error variance was continuously and significantly diminished by including the following variables RAN, N1 and VWFS (RAN: p=0.034; RAN and N1: p=0.005*; RAN, N1 and VWFS: p=0.001*). Accordingly, these three variables significantly discriminated poor and normal reading 2nd graders (Eigenvalue=2.23, canonical correlation=0.83, Wilks' Λ= 0.309, χ2(4)=15.84). The other variables PAbs, PAns and LK did not further contribute to classification. The leave-one-out cross-validation method yielded a correct classification of 94.1% (sensitivity: 100%; specificity: 90.9%). Additional analyses were performed by using a cut-off 40th percentile criterion (see SI2D) for grouping the children. In this way also the children of the gap group remained in the analyses. These subsidiary analyses converged with the reported core analysis and achieved a similar classification accuracy.

When repeating the core discriminant analysis with the left MTG (instead of VWFS) (see SI2C), this variable did not significantly improve the classification achieved by RAN and N1 (Eigenvalue=1.16, canonical correlation=0.73, Wilks' Λ= 0.464, χ2(4)=10.75). The leave-one-out cross-validation method therefore yielded a slightly poorer classification of 82.4% (sensitivity: 100%; specificity: 72.7%).

3.5 Discussion

In this study we combined behavioural, electrophysiological and functional MR measures collected in kindergarten to predict future reading outcome in 2nd grade. In addition to standard behavioural literacy screening tests used in non-reading kindergarteners, neuroimaging measures were collected from the same children after an eight week grapheme-phoneme association training (Graphogame) (Lyytinen et al., 2009; Lyytinen et al., 2007). Even though the children were still not able to read after the rather short training period, their basic grapheme-phoneme correspondence knowledge improved and initiated activation in neural networks for reading as reported in Brem et al. 2010. The EEG and fMRI data were recorded during

attempted explicit word reading/decoding vs. judging visual characteristics of symbol strings.

Table 3:
Multiple regression analyses using stepwise procedure.

		B	SE B	β
Step 1	Constant	-90.04	75.65	
	Receptive vocabulary	4.89	2.61	0. 47(*)
	PAbs	1.51	2.00	0.15
	PAns	3.79	3.37	0.21
	Post-training LK	-0.04	0.47	-0.02
	RAN	-0.83	0.66	-0.24
Step 2	Constant	14.03	72.18	
	Receptive vocabulary	1.94	2.38	0.19
	PAbs	2.83	1.70	0.28
	PAns	2.90	2.76	0.16
	Post-training LK	-0.49	0.42	-0.24
	RAN	-2.28	0.75	-0.65*
	N1 at LOT	-6.09	2.21	-0.61*
Step 3	Constant	18.10	50.00	
	Receptive vocabulary	1.98	1.65	0.19
	PAbs	2.28	1.19	0.22(*)
	PAns	3.92	1.93	0.22(*)
	Post-training LK	-0.31	0.25	-0.15
	RAN	-2.66	0.53	-0.76**
	N1 at LOT	-6.42	1.53	-0.65**
	VWFA ROI	-64.72	17.28	0.39**
Note: receptive vocabulary, subtest of Marburger Sprachverständnistest für Kinder, MSVT; PAbs, phonological awareness in a broad sense; Pans, phonological awareness in a narrow sense; Post-training LK, post-training knowledge of upper and lower case letters; RAN, rapid naming; LOT, left occipito-temporal electrode cluster; VWFS, ROI of the condition difference with centre at MNI x=-42, y= -54, z= -17 and radius = 5mm.				
Average R2=.65 ($p<0.05$) for step 1; $\Delta R2=.14$ ($p<0.01$) for step 2; $\Delta R2=.12$ ($p<0.01$) for step 3				
* $p<0.05$ ** $p<0.01$ (*) $p<0.10$				

3.5.1 Prediction of reading outcome with behavioural measures

In accordance with previous studies aimed at predicting dyslexia with behavioural assessments (Catts et al., 2001; Lyytinen et al., 2009; Maurer et al., 2009; Puolakanaho et al., 2007) we replicated the predictive potential of specific behavioural measures at kindergarten age for later reading outcome. Phonological awareness (Liberman et al., 1974; Snowling, 2000), rapid naming (Compton, 2000; Compton et al., 2001; Manis et al., 2000) and letter knowledge (Pennington and Lefly, 2001; Puolakanaho et al., 2007) measured in kindergarteners correlated with

reading in 2nd grade and together explained 51% of the variance. While RAN significantly improved classification of poor and normal reading 2nd graders, letter knowledge and phonological awareness did not contribute to this discrimination, even though letter knowledge has repeatedly been identified as an important indicator of later reading problems at preschool age (Pennington and Lefly, 2001; Puolakanaho et al., 2007), especially in consistent languages. One could reason that letter knowledge in previous studies was always assessed before specific literacy training (such as grapheme-phoneme training) thereby reflecting children's self-attained knowledge and thus serving as a more reliable predictor. But when using pre-training letter knowledge (SI2A) instead of post-training letter knowledge as predictor variable, a similar amount of variance was explained (54%). Only through substitution of post-training letter knowledge with the gain in letter knowledge through training, was a better prediction result achieved (59%, see SI2B). There is some evidence that phonological awareness is a poorer long-term predictor compared to rapid naming (Furnes and Samuelsson, 2009; Georgiou et al., 2008) but it seems to be important in early grades as also indicated by prediction analyses in our behavioural sample (see SI1). Another important predictor of reading is the child's home literacy environment encompassing various factors such as for example shared reading, parental encouragement, library visits and others (Burgess et al., 2002; Whitehurst and Lonigan, 1998). Examination of home literacy environment on reading achievement was not a main aim of this study and therefore we only recorded the number of books at the children's home to roughly estimate their literacy environment. Because no significant correlation between the number of books (children or parents) and the reading performance in second grade was found we did not further evaluate its predictive potential for our imaging sample. For our larger behavioural sample (see Table SI-1) a trend for a correlation between the number of the child's books and its reading performance was detected but inclusion of this measure in the hierarchical stepwise regression analysis did not improve prediction. This result, may not question the importance of home literacy environment for children's reading achievements but rather indicates that literacy environment should not be measured using solely one variable (Burgess et al., 2002; Whitehurst and Lonigan, 1998).

3.5.2 Neural activation to print and symbol processing

In accordance with our previous article (Brem et al., 2010), non-reading kindergarteners showed sensitivity to print over symbols in the form of an occipito-temporal negativity in the N1 time range (188-281ms) after learning the principles of grapheme-phoneme associations (Brem et al., 2010; Maurer et al., 2006). Correlations of letter knowledge measures with this left occipito-temporal activation in the N1 at LOT support its role in the development of print specificity. In accordance with the ERP measures, the whole brain analysis of the fMRI data also yielded print sensitive activation in the VWFS. The more pronounced activation to words than symbols in the VWFS appeared at a slightly lower and uncorrected statistical threshold in the data of the whole group. For the eleven kindergarten children who achieved normal reading scores in 2nd grade, however, the differential activation in the VWFS survived the cluster-extent corrected threshold. The correlation of print sensitivity within the VWFS ROI, and the gain of lower case letter knowledge, underlined the important role of this region for emerging literacy.

Previous studies showed that print sensitivity is diminished in young dyslexic children (Maurer et al., 2007) but may normalise after they have gained experience with reading (Maurer et al., 2011) although dyslexic adults also show deficient sensitivity (Helenius et al., 1999; Shaywitz and Shaywitz, 2005). Together with the recent finding of clear functional and structural alterations in the left occipito-temporal cortex (Raschle et al., 2011; Specht et al., 2009) of preschool children with a familial risk of dyslexia, these studies thus clearly point to the potential power of print sensitivity as an index for successful reading acquisition.

In line with our expectation, the differential N1 mean amplitude at kindergarten age significantly contributed to both the prediction and classification of poor and normal readers in 2nd grade and together with behavioural measures explained 67% of the variance in our group. Moreover, and in accordance with the above, print sensitivity measured as percent signal change in the VWFS also significantly improved the explained variance in reading skills at 2nd grade by 17%. A total of 84% of the variance in the reading skills of 2nd graders could thus be explained by behavioural, ERP and fMRI measures collected at kindergarten age. A preliminary discriminant analysis corroborated this result by yielding high sensitivity and specificity when using the same behavioural, ERP and fMRI measures in kindergarten to differentiate between future normal and poor reading children.

As a more explorative approach we also investigated (see SI2C) whether any area that exhibited significantly more pronounced activity to words than symbols in the whole brain analysis of kindergarteners would explain further variance. These areas largely belonged to the characteristic language network and included areas in the left and right frontal and temporal lobes. Only the area in the left middle temporal gyrus contributed to the prediction of future reading skills by explaining 78% of the variance in later reading skills (see SI2C) together with the behavioural and ERP measures. The activity in the middle temporal gyri has been related to phonological processing and more specifically may directly reflect grapheme-phoneme decoding, a process that is affected in poor reading children (Jobard et al., 2003; Rumsey et al., 1997; Sakurai et al., 2000). However, middle temporal areas have also been implicated in accessing lexical and semantic information in terms of a sound-to-meaning interface network (Hickok and Poeppel, 2000, 2004, 2007). In their meta-analysis Vigneau and collaborators (Vigneau et al., 2006) have attributed a role in semantic processing and verbal knowledge to the left middle temporal area. Even though our children were still not able to read and classify the words, as confirmed by the high rate of omissions, it is highly likely that they were searching for a meaning: When the children pressed a button, their response was well above chance. It seems that the children tried to decode the words but often remained indecisive, answered too late and responded only, when they were quite sure about the meaning of the word. Therefore it seems reasonable to assume that some children were able to identify a few words. The contribution of the left middle temporal gyrus in the prognosis of reading outcome may reflect the development of a sound-to-meaning interface.

The activation in the left inferior frontal gyrus has repeatedly been associated with phonological processes as shown by the meta-analysis of Vigneau (Vigneau et al., 2006) or a series of studies using either auditory (Booth et al., 2007; Cao et al., 2006; Ruff et al., 2008) or visual tasks (Bach et al., 2010; Bitan et al., 2006; Poldrack et al., 1999). Its pronounced activation is in line with the well established view that phonological processes are especially important at the beginning of reading acquisition (Coltheart et al., 2001; Ehri, 1998). Finally, the activation in the medial frontal gyrus could reflect the automatic allocation of attention to words (Peng et al., 2003). Whether activation in these areas might contribute to the prediction of reading later in development needs to be clarified by future studies.

Interestingly, the frontal and temporal areas exhibiting more pronounced activation to words in our explicit word processing task did not show differential activity when an implicit task was used (Brem et al., 2010), which is in contrast with adult readers or normal reading school children who also show this differentiation during implicit word processing (Brem et al., 2009; Price et al., 1996; Vinckier et al., 2007). This might indicate on the one hand that children at least tried to read after receiving the explicit instruction, but more likely suggests that only specific stages of word processing are automatized at this early phase of reading acquisition. Viewed the other way round, the implicit print processing task highlighted the emerging print sensitivity in the occipito-temporal cortex acquired when learning grapheme-phoneme correspondences, in line with the letter-specific response reported for 4-6 year-old non-reading children in a recently published study (Cantlon et al., 2011) investigating category-specific cortical representations in young children.

3.5.3 Limitations of the present study

In this study we aimed to follow a homogenous sample of healthy young children within a narrowly defined educational age range, and with strict criteria regarding confounding factors such as their native language. The very young age of the participating children, the application of different imaging techniques within the same children and the longitudinal design of the study resulted in a relatively small but well defined sample (n=19) for combined behavioural, EEG/fMRI prediction analyses. We acknowledge that the small sample size in this study has important implications for the validity and reliability of the statistical analyses and their interpretation. The use of small sample sizes may result in overfitting the data and overstressing a characteristic of a specific group. Such models thus may fail to provide valid predictions in a sample other than the one used to specify the model. Therefore, the high sensitivity and specificity found in the discrimination analyses as well as the regression analyses should be interpreted with caution and regarded as preliminary results despite crossvalidation. Nevertheless, the results in this particularly valuable sample are important and correspond nicely to the hypothesis based on previous studies that print sensitivity can contribute to the prognosis of reading outcome at an early age. Our preliminary analyses thus show the potential of specific imaging measures in predicting early reading outcome, i.e. before children learn to read at

school. Predictions about future reading skills with neuroimaging measures have already been demonstrated for preschool (Raschle et al., 2011; Specht et al., 2009) and older children by using structural and functional MR measures (Hoeft et al., 2011; Hoeft et al., 2007) or for very young children based on ERP data on auditory processing (Guttorm et al., 2010; Guttorm et al., 2005; Maurer et al., 2009; Molfese, 2000; Benasich et al., 2006). Our data are thus in line with a series of recent articles that demonstrate the potential of neuroimaging measures to improve prediction. Given the limited group sizes in this study, replication studies with larger samples are certainly needed to corroborate the present results.

To address the problem of the small samples in the discriminant analysis, the analysis was repeated (see SI2B) after inclusion of the two children with "intermediate" (between the 25th and the 40th percentile) reading skills, and a similar classification of "better" (>40th percentile) and "poorer" (<40th percentile) readers was achieved.

Another limitation is the selection of an explicit word processing task in children who were not able to read as confirmed by the high rate of omissions for word stimuli. In contrast to our implicit paradigm described elsewhere (Brem et al., 2010), our intention here was not only to retain children's attention on the stimuli but also to stimulate in-depth letter string processing to examine precursor processes of reading such as letter decoding. The condition difference in the ERP, and the differential fMRI activation within the well known reading network substantiated that this aim was achieved.

3.6 Conclusion

No study to date has combined neuronal activity measures acquired with different imaging techniques and behavioural measures to improve the prognosis of later reading skills. Because ERP and fMRI are sensitive to different aspects of information processing their combination might critically advance prediction of reading skills as demonstrated in the present article. In our sample of nineteen children, the print sensitivity of the N1 and the VWFS together with behavioural data in kindergarten achieved a remarkably accurate prediction of reading skills in the same children two years later. Even though the present results need to be confirmed by future studies with larger sample sizes, our preliminary results provide evidence

for the enormous potential of combining functional markers from different imaging techniques for pre-dating reading outcome at preschool age. Certainly, the approach in our study is time-consuming and expensive, but its application could yield a tool that more precisely predicts future reading outcome (competence) at preschool age. Particularly children with an elevated familial risk for future reading problems could be screened before school, and if required, receive targeted therapy before reading problems and negative school experiences emerge.

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3.8 Supplemental information

SI1 Prediction analysis with the behavioural sample

Subjects and groups

Below, we report the results of a supplemental prediction analysis for the larger behavioural sample which included all 40 children (mean age 6.4±0.3 years, 20 girls, 4 left-handed) who completed at least the behavioural assessments in kindergarten and the behavioural follow-up in 2nd grade. In accordance with the analysis of the main text, the kindergarten children were retrospectively grouped into poor (PR, <25th percentile in SLT reading test, n=15, 7 girls, 6.36±0.31) and normal reading children (>40 percentile, n= 20, 10 girls, 6.44±0.37) based on their performance in the reading

test in 2nd grade. Five children showed “intermediate reading skills” and belonged to the gap group.

Behavioural data

The group comparisons as well as the correlation of each behavioural kindergarten measure with the 2nd grade reading score are summarized in Table SI-1. NR compared to PR differed significantly in PAbs, pre-training lower case LK, post-training lower case LK, post-training LK total, literacy environment of the child and tended to differ in pre-training LK total. The groups also tended to differ in the CBCL attention score with the NR scoring slightly higher than the PR but still well below the sub-clinical range. The correlations with 2nd grade reading score yielded significances for PAbs, all measures of LK and trends for ARHQ, IQ, RAN and literacy environment of the child. Training time significantly correlated with letter knowledge (post-training upper case LK p=0.028, r=0.351) and especially with letter knowledge gain, which has been calculated as post-training minus pre-training LK (LK gain upper case p=0.017, r=0.379; LK gain lower case p=0.001*, r=0.500; total LK gain p=0.001*, r=0.530), implying that the longer the children played, the more grapheme-phoneme correspondences they learned as already reported in (Brem et al. 2010).

Multiple linear regression analyses

Behavioural measures in kindergarten were entered as predictor variables in the multiple regression analyses whenever they significantly correlated with the reading score in 2nd grade (Table SI-1: PAbs, all measures of LK). To minimize the total number of behavioural predictors we only included one letter knowledge measure (total post-training LK).

Hierarchical stepwise method: The behavioural measures significantly predicted reading outcome (R=.54, F(2,37)=7.8, p=0.002*) and explained 26% (adjusted R square) of the variance in the 2nd grade reading score. According to the standardized β-coefficients, PAbs (p=0.016*) and post-training LK (p=0.033) significantly contributed to the prediction in the model, wherefore both variables were chosen as predictor variables for a subsequent discriminant analysis to distinguish NR (n=20) and PR (n=15). Note, we repeated this analysis and included also the number of books of the children as a predictor variable due to the trend (p=0.059) found for the

correlation with 2nd grade reading performance (Table SI-1). The prediction of the reading outcome (R=.57, F(3,36)=5.63, p=0.003*, adjusted R square: 26.3%), however, almost remained the same: The inclusion of this measure thus did not yield a better prediction.

Discriminant analysis: The five children exhibiting intermediate reading scores in between the 25*th* and the 40*th* percentile (referred to as gap group) were not included in the subsequent analysis. The discriminant analysis for the behavioural sample showed, that error variance was significantly diminished by PAbs (p=0.002*) only. This variable significantly discriminated poor and normal reading 2nd graders (Eigenvalue=0.35, canonical correlation=0.51, Wilks' Λ= 0.741, χ2(4)=9.76). The leave-one-out cross-validation method yielded a correct classification of 68.6% (sensitivity: 73.3%; specificity: 65%).

Table SI-1:
Group comparison for demographics and behavioural tests for the larger group.

	Groups according to reading scores in 2nd grade			**n=40**
Behavioural measures in kindergarten	**NR (n=20) (>40Percentile)** Mean ± SD	**PR (n=15) (<25Percentile)** Mean ± SD	***P (groups)***	***P one-sided Pearson's correlation with reading score in 2nd grade***
Reading score in 2nd grade (words per minute score **SLT**; percentile)	70.03±17.20	11.54±7.79	***<0.001***	
Pretest age (years at behavioural assessment at home)	6.44±0.37	6.36±0.31	*0.502*	*0.153*
Attention score (**CBCL**)	50.30±7.92	45.53±6.34	*0.065*	*0.131*
IQ (Raven) (ss)	56.35±8.87	53.60±5.779	*0.304*	*0.220*
ARHQ (mean)	0.27±0.09	0.31±0.11	*0.336*	*0.100*
Training time (minutes)	317.23±131.17	327.82±146.17	*0. 827*	*0.401*
Rapid naming **RAN** (speed in seconds)	43.80±11.33	49.0±7.67	*0.135*	*0.077*
Receptive vocabulary (**MSVT**) (ss)	56.40±8.31	52.60±7.19	*0.166*	*0.185*
Word comprehension (**MSVT**) (ss)	46.95±7.47	48.60±6.02	*0. 488*	*0.805*
BISC risk score	1.30±1.45	1.80±1.01	*0.263*	*0.210*

Phonological awareness (broad sense) **PAbs**	17.65±1.79	15.2±2.48	***0.002***	***0.002****
Phonological awareness (narrow sense) **PAns**	18.55±2.14	17.53±2.67	*0.220*	*0.136*
Pre- training **LK** (lower case)	7.40±7.26	3.4±2.03	***0.028***	***0.005***
Pre- training **LK** (upper case)	11.45±8.76	7.93±5.18	*0.148*	***0.012***
Pre- training **LK** (total)	18.85±15.53	11.33±6.28	*0.060*	***0.006***
Post-training **LK** (lower case)	16.05±7.57	10.2±6.5	***0.022***	***0.003***
Post-training **LK** (upper case)	17.10±7.40	13.2±5.93	*0.103*	***0.008***
Post-training **LK** (total)	33.15±14.56	23.4±12.12	***0.043***	***0.004***
Socio-economic status	16.6±3.57	15.7±3.22	*0.448*	*0.453*
Number of books parents	4.45±1.0	4.13±1.19	*0.398*	*0.985*
Number of books child	4.60±0.82	3.60±1.12	***0.007***	*0.059*

Note: All behavioural measures have been collected before Graphogame training except for the post-training letter knowledge measures and training time.

CBCL Child Behaviour Checklist; **ARHQ** Adult Reading History Questionnaire; **MSVT** Marburger Sprachverständnistest für Kinder; **BISC** Bielefelder Screening zur Früherkennung von Lese-Recht-schreibschwierigkeiten; **Number of books** categorical measure (parents: 0=no books; 1=1-10 books; 2=11-50 books; 3=51-100 books; 4=100-200 books; 5= more than 200 books; child: 0=no books; 1=1-10 books; 2=11-20 books; 3=21-30 books; 4=31-50 books; 5= more than 50 books)
Ss standard score (T = 50, SD = 10)
* Bonferroni corrected

SI2 Supplementary analyses for the imaging sample

A) Pre-training letter knowledge as predictor

The behavioural measures with pre- instead of post-training LK as predictor variable in the imaging sample predicted reading outcome (R=.82, F(5,13)=5.1, p=0.008) and explained 54% of the variance. The N1 print sensitivity did not explain additional variance but the VWFS print sensitivity added significantly to the prediction (p=0.024) and increased the amount of explained variance to 68% (Table 3).

According to the standardized β-coefficients (Table 3) the RAN (p=0.040) and the VWFS (p=0.024) significantly contributed to the prediction in our model, wherefore they were chosen as predictor variables for a subsequent discriminant analysis to distinguish NR and PR.

The stepwise procedure of the discriminant analysis in the imaging sample showed that error variance was only significantly diminished by RAN (p=0.034). RAN

significantly discriminated poor and normal reading 2nd graders (Eigenvalue=0.36, canonical correlation=0.52, Wilks' Λ= 0.734, χ2(4)=4.485). The leave-one-out cross-validation method yielded a correct classification of 64.7% (sensitivity: 66.7%; specificity: 63.6%).

B) Gain in letter knowledge (post vs. pre grapheme-phoneme training) as predictor

The behavioural measures including letter knowledge gain significantly predicted reading outcome (R=.84, F(5,13)=6.1, *p*=0.004*) and explained 59% of the variance. When adding N1 print sensitivity the explained variance significantly increased to 71% (*p*=0.025). The VWFS print sensitivity also added significantly to the prediction (*p*=0.001*) and explained 88% of the variance.

The standardized β-coefficients of the RAN (*p*<0.001*), LK gain (*p*=0.047), PAns (*p*=0.008), the condition difference of the N1 (*p*=0.001*) and the VWFS (*p*=0.001*) significantly contributed to the prediction in our model and were entered in the discriminant analysis.

The stepwise procedure of the discriminant analysis in the imaging sample showed, that error variance was significantly diminished by each included variable (RAN: *p*=0.034; RAN and N1: *p*=0.005*; RAN, N1 and VWFS: *p*=0.001*) and thus largely corresponded to the results reported in the main text.

C) Multiple regression analysis including the functionally defined ROIs

When substituting the VWFS ROI in the multiple regression analyses by each of the functionally defined ROIs (left or right medial frontal gyrus (lMFG, rMFG), left or right middle temporal gyrus (lMTG, rMTG), left inferior frontal gyrus (lIFG)), only the left MTG significantly added explained variance over behavioural and EEG measures.

The behavioural measures significantly predicted reading outcome (R=.80, F(5,13)=4.7, *p*=0.011) and explained 51% of the variance. When adding N1 print sensitivity the explained variance increased significantly to 67% (*p*=0.017). Further, the left MTG print sensitivity also significantly contributed to the prediction (*p*=0.027) and increased the explained variance to 78%.

The standardized β-coefficients of the RAN (*p*=0.001*), the condition difference of the N1 (*p*=0.002*) and the MTG (*p*=0.027) significantly contributed to the prediction in our model and were entered in the discriminant analysis. The left MTG, however, did

not significantly improve classification into NR and PR over behavioural and ERP N1 measures.

D) Discriminant analysis with a group cut-off at the 40th percentile in the reading test

The same predictor variables as in the main analysis were entered in this supplemental analysis with the imaging group. The two children of the gap group with a reading score between the 25th and the 40th percentile now belonged to the group with poorer reading skills (n=8). In accordance with the main text the discriminant analysis with the stepwise procedure revealed that error variance was significantly diminished by each included variable (RAN: p=0.016*; RAN and LOT: p=0.001*; RAN, LOT and VWFA: p<0.001*), thus again the three variables significantly predicted reading score in second grade (Eigenvalue=2.27, canonical correlation=0.83, Wilks' Λ= 0.306, χ2(4)=18.37). The leave-one-out cross-validation method yielded a correct classification of 89.5% (sensitivity: 100%; specificity: 81.8%).

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4 GENERAL DISCUSSION

Using a multimodal approach the present thesis aimed at clarifying the neural basis of phonological processing related to poor reading in children and identifying the potential of neuroimaging measures for prediction of reading skills. Even though a considerable number of behavioural, EEG and fMRI studies on dyslexia and phonological processing already exists, little is known about brain processes at the very beginning of reading acquisition, when the problems of dyslexic children start to emerge. Furthermore it has not been studied yet whether early imaging measures captured by EEG and fMRI technique can improve prediction of poor reading over behavioural data alone. We therefore examined very young children, either non-reading kindergarteners or children in the middle of 2nd grade when they are in the beginning of formal reading instruction.

In beginning normal and poor readers we compared brain activation to demanding phonological processes evoked by covert word reading and subsequent mental letter substitution. Here we could clearly demonstrate that brain activation in left frontal language areas increased with reading skills and showed a more pronounced left lateralization in normal than in poor readers.

In kindergarteners we found emerging print sensitivity in the occipito-temporal cortex due to grapheme-phoneme correspondence training. By capturing functional and behavioural aspects of this emerging print sensitivity a critical contribution to the prediction of reading skills at school age was realised.

4.1 The combination of neuroimaging methods

This study included a multimodal brain imaging approach to take advantage of the complementary nature of EEG and fMRI. While ERPs reveal information about the exact timing of processing in the brain, fMRI yields detailed information about the spatial aspects of involved brain networks. The interpretation of ERP and fMRI results in combination is still challenging because different aspects (direct and indirect processes) are captured by the two techniques. Furthermore, the fMRI technique delivers poor temporal resolution (Menon et al. 1998) and the EEG

technique in turn delivers poor spatial information (Pascual-Marqui et al. 1994). However, this combination still provides important information by highlighting different aspects of cognitive processes, as they are measured through electric activity of large neuronal populations and blood perfusion changes respectively.

Before imaging studies with young children can be performed several circumstances have to be considered: More time has to be taken for instruction and demonstration. In addition to easier and less demanding tasks, acquisition duration (e.g. number of trials) should be kept to a minimum to maintain childrens attention. With neuroimaging measures such as EEG and fMRI, movement must be kept to a minimum in order to achieve acceptable data quality, however “keeping still” is very difficult for young children.

If good data quality is obtained through both EEG and fMRI in the same children, investigations can profit from the two techniques. Not only do the techniques provide information in terms of temporal and spatial processing but also in combination, as in our study, they could significantly improve prediction of reading skills in 2nd graders by measurements taken from kindergarten.

4.2. Phonological processing in beginning readers

With fMRI phonological processing was examined in children in 2nd grade and activation patterns were analysed and compared between normal and poor readers. The children performed a covert reading and mental letter substitution task. During substitution trials the first or last letter in a word had to be substituted by another letter, inducing phonological processes. In the control task, letters were substituted by the same letter triggering no additional phonological processes.

By comparing the activation induced by the control condition with the activation generated by the experimental condition, phonological manipulation skills of the children could nicely be demonstrated and located in a left inferior frontal (IFG) network. This result supports previous studies reporting frontal activity for demanding phonological processing (Booth et al. 2007; Cao et al. 2006; Shaywitz and Shaywitz 2005). Generally more left hemispheric activity in normal compared to poor reading 2nd graders was observed. This study thereby supports earlier investigations reporting enhanced IFG activation in normal readers vs. dyslexics (Cao et al. 2006; Georgiewa et al. 1999; Shaywitz et al. 2002) compared to investigators reporting

more left frontal activity in dyslexic children (Georgiewa et al. 2002; Temple et al. 2001). In the study of Temple and colleagues two letters were presented and in the two conditions the children either had to judge whether the letters rhymed or whether the same letters were presented (Temple et al. 2001). It has been argued that this task requires simple phonological processes compared to more demanding processes (Shaywitz et al. 1998) in tasks such as e.g. non-word rhyming (Shaywitz et al. 2002) or conflicting and non-conflicting orthographical and phonological trials (conflicting: similar orthography but different phonology – e.g. *pint and mint* or similar phonology but different orthography – e.g. *jazz and has*; non-conflicting: similar orthography and phonology – e.g. *gate and hate* or different orthography and phonology – e.g. *press and list* (Booth et al. 2008; Cao et al. 2006)). Such rhyming tasks or tasks including conflicting and non-conflicting orthographical and phonological trials can not be used with the German language as the German orthography is more transparent. We therefore designed a new demanding task in terms of phonological processing, the covert reading and mental letter substitution task. Both experimental conditions in our mental letter substitution task involved reading, memorizing a word/pseudoword as well as a lexical decision. Since an active manipulation of the sound structure of the memorised word was required only in the substitution condition, the contrast of both conditions nicely accentuates phonological processes and minimises e.g. processes involved in lexical or working memory. However, the IFG has also been reported to be important in other processes such as verbal working memory (Cohen et al. 1997). For this reason, we examined the relation of our IFG activation with the behavioural working memory measure (digit span). The non-significant correlation indicated that the influence of the working memory on the IFG activation in our task was minor. This result is not surprising considering the matched working memory load across conditions. We thus assume the inferior frontal gyrus to be specifically involved in phonological processes that are needed to build up a new phonological representation of a word after mental letter substitution. Besides the putative involvement of the working memory processes, in case of an implicit matching of the lexical status before and after the presentation of the letter, it is difficult to disentangle phonological and semantic processes. Generally, it is very difficult to design tasks measuring only one single process, especially in reading studies where several processes are confounded such as orthographic, phonological and semantic processes. It has been debated whether

hypoactivation of poor readers compared to normal readers might occur only when demands on phonological processes are high (Shaywitz et al. 1998). In contrast to our study, in the study by Georgiewa left frontal activation was enhanced in dyslexics (Georgiewa et al. 2002), but as slice thickness was 10mm, precise frontal activations presumably have been missed and could not overlap with our IFG. In addition, our results confirm the findings of early emergence of the left lateralization for language processing (Gaillard et al. 2001; Holland et al. 2007; Ressel et al. 2008). A more bilateral fronto-temporal activation pattern was found in poor readers and the activity of the right hemispheric IFG was found to be correlated with performance in behavioural phonological tasks. A closer look at this correlation revealed that especially poor readers with good phonological skills exhibited activity in the right IFG. Therefore, we suggest that the right frontal brain activity in poor readers reflects the recruitment of additional resources for decoding and accessing lexical information. Shaywitz and colleagues have also reported overactivation of right frontal areas in 7 to 18 year old poor readers and suggested that involvement of additional right hemispheric areas may represent a strategy to compensate for the deficits found in the form of hypoactivation in posterior networks (Shaywitz et al. 2002) involved in phonological, semantic and lexical processing. As our sample was very young we assume that right frontal compensatory mechanisms start to emerge very early during reading acquisition, presumably right at the beginning of reading instruction or even earlier. It is, however, still unclear whether the abnormal functional activation is caused by an underlying impairment of specific anatomical structures of the brain or by a failure to engage the normal set of areas involved in the reading network. The early brain-related differences between normal and poor readers in our study however indicate basic neural deficits in the functional reading networks. Further studies might answer the question, whether anatomical or functional neural differences in even younger children (pre-kindergarten) might serve as markers before school enrolment, which could be promising in terms of early and specific intervention programs. Thus the second part of this PhD thesis aims at identifying functional brain imaging measurements in kindergarteners that could improve prediction of future reading outcome.

4.3. Prediction of poor reading

To predict reading outcome in 2nd grade, we used brain activation and performance measures obtained after a brief computerized grapheme-phoneme correspondence training called Graphogame (Lyytinen et al. 2009; Lyytinen et al. 2007) in kindergarten: With training, the children in kindergarten gained basic letter knowledge as well as preliminary competencies in word decoding. After the training EEG and fMRI measures were recorded during explicit reading attempts of the kindergartners. These reading attempts activated print specific regions in the brain which were further analysed in terms of its contribution to the prediction of future reading. The behavioural and neural measures in kindergarten were also explored regarding their potential to discriminate poor and normal readers at school age.

Several studies have linked future reading outcome with behavioural measures (Catts et al. 2001; Puolakanaho et al. 2007) or behavioural measures with additional electrophysiological (Guttorm et al. 2005; Guttorm et al. 2003; Maurer et al. 2009; Molfese 2000), structural and functional measurements (Hoeft et al. 2007; Semrud-Clikeman et al. 1996). Besides behavioural data reported to be predictive for reading outcome (Liberman et al., 1974; Snowling, 2000; Compton, 2000; Compton et al., 2001; Manis et al., 2000; Pennington and Lefly, 2001; Puolakanaho et al., 2007), we have chosen additional, specific measurements from EEG *and* fMRI to examine their potential for prediction of reading success. In EEG studies investigating print specific effects in children, a left occipito-temporal negativity in the N1 time range showing more activity for words as compared to symbols has been revealed, which has been interpreted as print sensitivity (Brem et al. 2010; Maurer et al. 2006). In our study the kindergarteners knew some letters after training, they tried to decode the presented words letter by letter in order to build a phonological representation and eventually access the word meaning from the phonological lexicon. Evolving sensitivity to print over symbols in the N1 of the left occipito-temporal cortex was found also in our kingergartners after grapheme-phoneme training. Further, corresponding to this print-sensitive left occipito-temporal negativity in the ERP, activity in the visual word form system of the left occipito-temporal cortex was revealed by fMRI (Brem et al. 2010; Brem et al. 2006; Cohen et al. 2000; van der Mark et al. 2009). Other investigators indicated that dyslexic children show diminished print sensitivity or functional and structural alterations in this left occipito-temporal area (Maurer et al., 2007; Raschle

et al., 2011). Given the evidence for the crucial role of print sensitivity in the occipito-temporal cortex for learning to read, measures of print sensitivity at preschool age seemed promising to predict reading outcome later on.

Together with the behavioural data (receptive vocabulary, phonological awareness, letter knowledge, rapid naming) in our rather small (n=19) but well defined, homogenous sample of healthy young children these additional print sensitivity measures from fMRI and ERP significantly contributed to prediction of reading (words per minute score) in 2nd grade and together with behavioural precursor skills explained 84% of the variance. The inclusion of neuroimaging measures thus critically improved prediction of reading outcome in 2nd grade over behavioural data alone. When the same kindergarten measurements were entered in a discriminant analysis, a convincingly accurate classification of poor and normal readers was achieved in the 2nd grade. Due to the limited sample size in our study and its implications for the validity and reliablility of the statistical analyses these interesting results have to be interpreted with caution and certainly need to be confirmed by further studies. Still, the results are important and correspond nicely to the hypothesis based on previous investigations that print sensitivity can contribute as potential predictor for reading success at an early age.

4.4. Conclusion

Several studies to date have provided interesting and meaningful findings in terms of dyslexia. But beside various approaches using different techniques and tasks with either children or adults, many questions still remain open. However, there is consent on genetic causes of dyslexia (Cardon et al. 1994; Galaburda et al. 2006; Hallgren 1950; Harlaar et al. 2005) as well as on the core deficit, namely a phonological processing impairment in children with reading problems (Ramus 2003; Torgesen et al. 1994). These phonological processing deficits result from poor phonological awareness skills (Bradley and Bryant 1983; Ramus 2003). By imaging studies phonological processes have often been related to left frontal activation (Booth et al. 2007; Cao et al. 2006; Gross-Glenn et al. 1991; Paulesu et al. 1996) and also in our study left frontal activation in the inferior frontal gyrus has been demonstrated i) when beginning readers in 2nd grade performed a demanding task requiring phonological

processing as well as ii) by initial attempts in grapheme-phoneme decoding and blending as seen in the fMRI activation difference of word vs. symbol processing in kindergarteners. Additionally, normal readers in the 2nd grade showed more involvement of the left hemisphere and especially the IFG in reading and phonological processes as opposed to poor readers who activated a more bilateral network for the same task. The specific left hemispheric frontal activity in normal readers probably reflects efficient processing of phonological transformations. The bilateral activity in poor readers, which was most pronounced in frontal and temporal areas in turn has been interpreted as compensation, as more effort was required to perform the same operations in the task with the same accuracy. The differing neuronal patterns between the children only 1.5 years after starting formal reading instructions indicate that plastic changes occur from the very beginning of learning to read when starting school. Thus, intervention should take place as soon as possible, preferably even before school starts, wherefore early prediction and identification of children with an increased risk for a poor reading outcome is a general aim. These children could then be supported with targeted training programs even before school enrolment. To persue this ambitious aim of early prediction our second study was conducted. Also other researchers have studied early prediction using behavioural (Catts et al. 2001; Puolakanaho et al. 2007), electrophysiological (Molfese 2000; Guttorm et al. 2001) or fMRI (Raschle et al. 2010) data alone. Some researchers have combined behavioural data with either electrophysiological or fMRI data (Guttorm et al. 2005; Guttorm et al. 2003; Maurer et al. 2009; Molfese 2000; Hoeft et al. 2007; Semrud-Clikeman et al. 1996). For the first time we have combined behavioural data with both imaging techniques and thereby included the well described left occipito-temporal cortex for developing print sensitivity in our prediction analysis. By taking into account behavioural predictors as well as neurophysiological and functional aspects of a beginning reading process a high classification accuracy was achieved. Even though an early screening of the children for diagnosing (a high risk of) dyslexia to date is not yet feasible, our results are still very interesting particularly for families with an elevated risk. Of course, further studies including more children are needed to confirm these results, improve prediction and develop a screening method with high sensitivity/specificity. By advancing and establishing a screening method children (e.g. with a familial risk) could be diagnosed early and interventions could start right at the beginning of school to prevent them from

developing unfavourable strategies, reading problems and negative school experiences.

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6. CURRICULUM VITAE

Silvia Bach
Höhtalstrasse 23
5408 Ennetbaden
Switzerland
Phone: +41 (0)76 391 11 84
viabach@gmx.net

Date of Birth	January 23, 1979
Place of Birth	Baden, Switzerland
Nationality	Croatian / Swiss

Education

2007 – 2011	Ph.D. thesis at the Brain Mapping Lab of the Department of Child and Adolescent Psychiatry, University of Zurich, Switzerland
2000 – 2005	Studies in Neuropsychology (Prof. rer. Nat. L. Jäncke) at the University of Zurich, Switzerland
1995 – 1999	Academic Upper Secondary School, Baden, Switzerland
1991 – 1995	Lower Secondary School, Wettingen, Switzerland
1986 – 1991	Primary School, Neuenhof, Switzerland

Employment

2009 - 2011	40% Neuropsychologist at the Kinderklinik, Kantonspital Aarau
01.2007 -	Neuropsychologist at the Zentrum für psychologische Beratung, Basel (case wise)

Trainings and projects

06.2005	'40th microgravity campaign'; ESA (European Space Agency) Bordeaux, France
11.2004 – 01.2005	Training as school psychologist, Olten, Switzerland
07.2004	'7th student parabolic flight campaign'; ESA Bordeaux, France
02.2004 – 04.2004	Neuroscientific training, Institute of Neuropsychology, Zürich, Switzerland
07.2003 – 08.2003	Training at the Psychiatric Clinic Königsfelden, Switzerland
03.2000 – 06.2000	English training, Santa Barbara, UCSB, United States of America
09.1999 – 12.1999	French training, Lausanne, Switzerland
03.2004 – 07.2004	Tutorial work, Institute of Neuropsychology, Zürich, Switzerland

7. PUBLICATIONS

Bach, S., Brandeis, D., Hofstetter, C., Martin, E., Richardson, U., Brem, S., 2010. Early emergence of deviant frontal fMRI activity for phonological processes in poor beginning readers. NeuroImage 53 (2), 682-93.

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